http://www.epa.gov/oppt/newchems/chemcat.htm

TSCA NEW CHEMICALS PROGRAM

(NCP)

CHEMICAL CATEGORIES

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Note on Test Guidelines Cited in this Document:

This document contains references to test guidelines that originally appeared in title 40, chapter I, subchapter R of the Code of Federal Regulations (CFR). Since that time, the "OPPTS Harmonized Test Guidelines" have been developed by EPA's Office of Prevention, Pesticides and Toxic Substances for use in the testing of pesticides and toxic substances, and the development of test data that must be submitted to the Agency for review under Federal regulations. These guidelines can be found at http://www.epa.gov/docs/OPPTS_Harmonized/. Until we fully update all the references contained within this categories document, you can find any new OPPTS guideline that corresponds to an old CFR citation. For example, the fish acute toxicity test at 40 CFR 797.1400 has been replaced by OPPTS 850.1075, and Ready Biodegradability at 40 CFR 796.3180, etc. has been replaced by OPPTS 835.3110.

Disclaimer:

EPA's Office of Pollution Prevention and Toxics (OPPT) groups chemicals with shared chemical and toxicological properties into categories so that PMN reviews are facilitated. PMN submitters and EPA reviewers benefit from the accumulated data and past decisions represented by a category. EPA considers all PMNs, including new chemical substances which fall within such categories, on a case-by-case basis and uses the most appropriate structural analogue to support any concerns for health or environmental effects. For any new chemical substance, if EPA determines, under TSCA section 5(e), that the substance "may present an unreasonable risk of injury to health or the environment," the PMN substance can be subjected to appropriate control actions and/or testing under TSCA section 5(e). This "may present" finding is developed through the application of category-based or chemical-by-chemical assessment of hazard endpoints and case-specific exposure assessment.

The categories included in this compilation represent chemicals for which sufficient assessment experience has been accumulated so that hazard concerns and testing recommendations vary little from chemical to chemical within the category. Thus, these categories do not necessarily represent the chemicals of greatest concern to the Agency. By the same token, the categories are also not intended to be a comprehensive list of all substances that may be subject to further action in the New Chemicals Program.

If a new chemical substance is structurally similar to a substance for which EPA has positive toxicity data and there is sufficient exposure, EPA may regulate that substance under section 5(e) of the Toxic Substances Control Act (TSCA) based on its potential unreasonable risk. The hazard potential of a PMN substance is dependent on the molecular weight of the compound, the presence/absence of activating/deactivating substituents, other physical/chemical properties, and the likely route of exposure. Typically, concerns are confined to chemicals with molecular weights <1,000 whenever inhalation exposure to humans or environmental release is expected, and to species <500 when dermal exposure to humans is expected.

Additional information on testing conditions and testing options for specific PMN chemical substances that appear to fall within one of these categories is available by contacting the New Chemicals Branch at 202-260-3725 or the TSCA Hotline at 202-554-1404. This is to serve only as a guide for PMN submitters. PMN submitters are urged to have protocols and testing schemes evaluated by the New Chemicals Program prior to commencing testing on a PMN substance. However, under no circumstance does such an evaluation mean that the new chemical substance is not subject to further review during any TSCA section 5 review period for the PMN substance or that additional testing or regulatory action may not be recommended. Finally, even if EPA does not make the potential unreasonable risk finding for a new chemical substance, the Agency may still recommend the use of engineering controls or personal protective equipment to reduce exposures in the workplace if the PMN substance is a potential irritant or sensitizer.

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Category: <u>Acid Chlorides</u> Environmental Toxicity

Definition. This category includes carbonyl chlorides (R-C[=O]Cl) and sulfochlorides (R-S[=O]Cl) where R may be either aliphatic or aromatic. Toxicity is limited by the fact that this class of compounds hydrolyzes and also, probably, if the octanol/water partition coefficient (Kow) is above a log Kow value of 8. It has been assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will probably be excluded in the future once this assumption is confirmed with toxicity information. However, toxicity information is needed to confirm this assumption.

Hazard Concerns. Acute toxicity for three members of this category are available and all have been shown to be moderately toxic to aquatic organisms (i.e., acute toxicity values between 1 and 100 mg/L): benzoyl chloride, fish 96-h LC50 = 35.0 mg/L, an aromatic dicarboxyl dichloride, fish 96-h LC50 = 6.2 mg/L, and benzene sulfochloride, fish 48-h LC50 = 3.0 mg/L. All of these tests have been done with the static method using nominal concentrations. It is unclear just how acid chlorides are toxic to aquatic organisms. It is known that acid chlorides hydrolyze to the carboxylic/sulfonic acid and HCl. It is not known if the toxic effect is the result of (1) absorption of the acid chloride and hydrolysis within the membrane, or (2) the HCl produced from the hydrolysis. It is known that the carboxylic/sulfonic-acid hydrolysis products are of low toxicity.

Boundaries. There are no known lower boundaries. The upper boundaries will be based on K_{ow} and MW when enough information is obtained. In general, when the log K_{ow} value is < 8, the environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log K_{ow} is > 8, testing will be requested until enough information is obtained to determine whether these compounds will have no toxic effects at saturation. Generally, members of this category will have MWs of less than 1000 but testing of members with a MW > 1000 may be requested to confirm whether acid chlorides have to be absorbed to be toxic.

General Testing Strategy. The testing strategy for acid chlorides will consist of two steps. (1) Hydrolysis as a function of pH at 25 °C (40 CFR 796.3500) will be recommended. Depending on the outcome of this environmental fate testing and reassessment, (2) the aquatic base set of environmental toxicity tests will be recommended for aquatic exposures with the fish acute toxicity test done once or twice.

Chronic toxicity testing for aquatic organisms include: the fish early life state toxicity test, the daphnid partial life cycle toxicity test and the algal toxicity test.

The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm acute toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

October, 1990

Category: <u>Acid Dyes and Amphoteric Dyes</u> Environmental Toxicity

Definition. Organic dyes are divided into four classes depending on the type of electronic charge of the dye: nonionic (neutral dyes); anionic (negative charge or acid dyes); cationic (positive charge) dyes; and amphoteric (mixture of positive and negative charges on same molecule) dyes. Nonionic or neutral dyes are assessed as neutral organic chemicals for which there is a separate category description, and cationic dyes also have a separate category description. Amphoteric dyes are assessed either as cationic or anionic dyes depending on dominant net charge.

Hazard Concerns. Analysis of over 200 acid dyes (Auer et al. 1990, Nabholz 1990, Sigman et al. 1983, Tonogai et al. 1979, Little and Lamb 1972, ADMI 1974) have indicated that some monoacid and diacid dyes can show moderate to high toxicity (i.e., acute values < 100 mg/L and < 1 mg/L) to fish and aquatic organisms. Dyes with three or more acid groups showed low toxicity (i.e., acute values > 100 mg/L) towards fish and invertebrates. Some metal chelated dyes, i.e., Al, Co, Cr, Fe, have shown moderate toxicity towards fish and daphnids and the toxicity has not been explained by the residual free (un-chelated) metal ion in the dye product. All acid dyes showed moderate toxicity towards green algae. Analysis of available data (Auer et al. 1990, Nabholz 1990) has suggested that effects to algae were not the result of direct toxicity but represented an indirect effect due to shading. Senior regulatory decision-makers in OPPT (then OTS) decided in 1988 that the risk to algae from indirect (shading) toxicity was not an unreasonable risk for two main reasons: (1) algae grew quickly as soon as the dye was diluted, and (2) the release of colored effluents in the U. S. generally results in immediate complaints by citizens to their local authorities, e.g., county and state governments. The rapid response by the public generally results in quick regulatory action by local officials.

Since there is no SAR for acid dyes (Auer et al. 1990), hazard profiles for monoacid dyes are developed using measured data or data for the nearest analog(s).

Boundaries. Acids dyes must have some water solubility and molecular weights generally need to be near or below 1000.

General Testing Strategy.

I. <u>Release to Aquatic Ecosystems</u>:

Tier 1. Because of the above boundary conditions, and the need to assess human exposure as well as environmental toxicity, if there is insufficient knowledge about the water solubility of the dye, then it should be measured (40 CFR §796.1860). The fish and daphnid acute toxicity tests from the aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR §797.1400) and daphnids (40 CFR §797.1300) will be done using the flow-through method with measured concentrations, and effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations.

If there is no significant risk from the PMN after the results of the fish and daphnid acute toxicity tests have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Direct and Indirect Photolysis Screening Test (40 CFR 796.3765). If $t½ \leq 2$ days, go to Tier 3; if $t½ > 2$ days, go to Tier 4.

Tier 3a. If $t½ \leq 2$ days and photolysis products are known and/or identified, then assess photolysis products for environmental hazards.

Tier 3b. If $t½ \leq 2$ days and photolysis products are not known and/or identifiable, then prepare a stock solution of PMN using the standard humic-containing solution described in the direct and indirect photolysis screening test [40 CFR 796.3765 (b)(2) and (c)(2)], expose to sunlight for at least 6 half-lives (t½), and test photolysis products for toxicity with most sensitive species from environmental base set.

Tier 4. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR 797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; and statistical analysis of effective concentrations at days 7, 14, 21, and 28.

Daphnid chronic toxicity testing (40 CFR 797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21.

Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation	40 CFR 796.3100
Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

II. Release to Terrestrial Ecosystems:

The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

References.

American Dye Manufacturers Institute, Inc. (ADMI), 1974, "Dyes and the Environment: Reports on Selected Dyes and Their Effects," Vol. II, ADMI, New York.

Auer, C.M., Nabholz, J.V. and Baetcke, K.P., 1990, "Mode of Action and the Assessment of Chemical Hazards in the Presence of Limited Data: Use of Structure-Activity Relationships (SAR) under TSCA, Section 5," Environmental Health Perspectives, Vol. 87, pp. 183-197.

Little, L.W. and Lamb J.C., III, 1972, "Acute Toxicity of 46 Selected Dyes to the Fathead Minnow, Pimephales promelas,"Final Report to the American Dye Manufacturers Institute,Inc., UNC Wastewater Research Center, Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina, Chapel Hill, NC.

Nabholz, J.V., 1990, "The OTS PMN ECOTOX Data Base: a Confidential Business Information (CBI) Collection of Environmental Toxicity Data from New Chemical Submissions Under Sec. 5," Unpublished, Environmental EffectsBranch, Health and Environmental Review Division (TS-796),U. S. Environmental Protection Agency, Washington, DC.

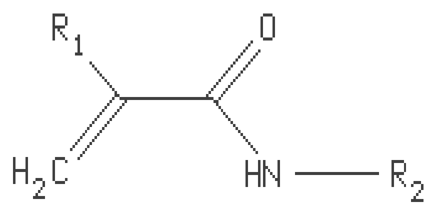
Sigman, C.C., Helms, C.T., Papa, P.A., Atkinson, D.L., Doeltz, M.K. and Winship-Ball, A., Jan. 1983, "Anthraquinone Dyes and Related Chemicals: Review and Assessment of Potential Environmental and Health Aspects," Final Report to the Dyes Environmental and Toxicology Organization, Inc., SRI International, Menlo Park, CA.

Tonogai, Y., Ito, Y., Iwaida, M., Tati, M., Ose, Y. and Sato, T., 1979, "Studies on the Toxicity of Coal-Tar Dyes. II. Examination of the Biological Reaction of Coal-Tar Dyes to Vital Body," The Journal of Toxicological Sciences, Vol. 4, pp. 211-219.

July, 1991; revised June, 1994

Category: <u>Acrylamides</u> Human Health and Environmental Toxicity

Definition. Any new chemical with the following structure is considered to be a member of the category:



R1 = H (acrylamides)

= CH3 (methacrylamides)

R2 = anything

A typical acrylamide in the new chemical program is used as a monomer and has a molecular weight of ≤500. The acrylamides of greatest concern are those with a labile substituent, e.g., methylol acrylamides, that may release acrylamide *per se* under metabolic conditions. For toxicity to aquatic organisms, there is a concern for all substituted acrylamides with molecular weights of <1000 and log Kow of <8.0.

Hazard Concerns. Based on analogy to acrylamide *per se*, members of the class are considered potential carcinogens, heritable mutagens, reproductive and developmental toxicants, and toxic to aquatic organisms. Acrylamides are also potential neurotoxins based on data for a number of low molecular weight acrylamides.

Boundaries. Structures with an acrylamide equivalent weight of ≥5,000 are presumed not to pose a hazard under any conditions. Typically, concerns are confined to those species with molecular weights <1,000 whenever inhalation (or environmental) exposure is expected, and to species <500 when dermal, but not inhalation, exposure to humans is expected.

Occupational Exposure Controls. Because acrylamides are expected to be absorbed via the dermal route, <u>glove permeation testing</u> conducted in accordance with standard ASTM testing protocols may be required, depending upon estimated workplace exposures and the hazard identified for the particular acrylamide submitted as a PMN.

<u>General Testing Strategy</u>.

Tier 1. To properly assess human and environmental toxicity or exposure, certain physical-chemical or environmental fate properties need to be measured:

water solubility (40 CFR §796.1860)
Kow (40 CFR §796.1570 or 40 CFR §796.1550)
vapor pressure (40 CFR §796.1950)
melting point-melting range (OECD 102 or OPPTS 830.7200)

Aerobic biodegradability can be determined using <u>one</u> of the following test guidelines, listed in approximate order of preference:

Aerobic aquatic biodegradation	40 CFR 796.3100
Modified Sturm test	40 CFR 796.3260
Closed bottle test	40 CFR 796.3200
Modified OECD screening test	40 CFR 796.3240
Modified MITI test (I)	40 CFR 796.3220
Modified AFNOR test	40 CFR 796.3180

The physical state and electronic charge of the PMN substance should also be reported.

Tier 2. EPA considers the following tests to be the most appropriate for acrylamides found to pose an unreasonable risk to human health:

- 90-day subchronic toxicity (40 CFR §798.2650) with functional observational battery (40 CFR §798.6050) and neuropathology (40 CFR §798.6400).

- A rodent dominant lethal assay (40 CFR §798.5450). If positive, a rodent heritable translocation test (40 CFR §798.5460) would be the appropriate followup test.

- A 2-year carcinogenicity test (40 CFR §798.3300) in rats and mice.

To address environmental toxicity concerns, the following testing is recommended, for acrylamides with <u>log Kow <5</u>: acute aquatic toxicity testing in algae, daphnid, and fish. The acute toxicity tests for fish (40 CFR 797.1400) and daphnids (40 CFR 797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control <2 mg TOC/L; the highest treatment concentration on a mean measured-basis should equal the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

The algal toxicity testing (40 CFR 797.1050), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and

96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; and the highest treatment concentration on a mean measured-basis equal to the aqueous solubility limit. Solvent can be used to assist the PMN substance to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN substance beyond its aqueous solubility limit.

For acrylamides with log Kow >5 and <8, aquatic toxicity testing should be for chronic effects only: (1) fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing with rainbow trout (40 CFR 797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; and statistical analysis of effective concentrations at days 30, 45, 60, 75, and 90; (2) daphnid chronic toxicity testing (40 CFR 797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; and (3) algal toxicity testing (40 CFR 797.1050), with static methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; and the highest treatment concentration on a mean measured-basis equal to the aqueous solubility limit. Solvent can be used to assist the PMN substance to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN substance beyond its aqueous solubility limit.

November 1990; revised July 1993; revised October 1995

Category: <u>Acrylates/Methacrylates</u> Environmental Toxicity
(Human Health, case-by-case)

Definition. Any molecular structure containing one or more of the following reactive groups is considered to be a member of the class:

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                  O
                  ‖
- acrylate,  CH2=CH-C-O-

                     O
                     ‖
- methacrylate,  CH2=C-C-O-
                     |
                     CH3
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Hazard Concerns.

Human Health: As a result of testing conducted under an agreement between the Agency and the Specialty Acrylates and Methacrylates (SAM) Panel of the Chemical Manufacturers Association (CMA), EPA no longer controls new chemical acrylates or methacrylates as a category based on health concerns. However, if a new acrylate is structurally similar to a substance for which EPA has positive toxicity data, EPA may regulate that substance under TSCA section 5(e) based on its potential unreasonable risk. This will be done on a case-by-case basis and is expected to effectively eliminate most regulation of acrylates, especially higher molecular weight and polymeric substances. Despite the fact that EPA no longer expects to make a potential unreasonable risk to human health finding for many of the new acrylates, EPA still recommends the use of engineering controls or personal protective equipment to reduce exposures in the workplace in recognition of their potential as irritants and sensitizers.

Environmental Toxicity: The ecotoxicity of acrylates and methacrylates is a function of the octanol-water partition coefficient. They exhibit simple narcosis at log P's >5, but display excess toxicity at lower log P's. The toxicity of acrylates and methacrylates can be predicted by a QSAR (quantitative structure-activity relationship), although there are some members of the class such as allyl methacrylate that are significantly more toxic than predicted by the QSAR.

Boundaries. Typically, environmental toxicity concerns are confined to those species with molecular weights <1,000. Acute and chronic toxicity is possible at log P’s <5, and chronic toxicity is possible at log P’s <8.

<u>General Testing Strategy</u>

Tier 1. To properly assess environmental toxicity or exposure, certain physical-chemical or environmental fate properties need to be measured:

water solubility (40 CFR §796.1860)
log Kow (40 CFR §796.1570 or 40 CFR §796.1550)
vapor pressure (40 CFR §796.1950)
melting point-melting range (OECD 102 or OPPTS 830.7200)
aquatic biodegradation (40 CFR §796.3100).

The physical state and electronic charge of the PMN substance should also be reported.

Tier 2. To address environmental toxicity concerns, the following testing is recommended: acute aquatic toxicity testing in algae, daphnid, and fish (all tests using measured concentrations; algae: static method, daphnid and fish: flow-through method).

September, 1988; Revised July, 1993 and January, 1997.

Category: <u>Aldehydes</u> Environmental Toxicity

Aldehydes are a class of organic compounds characterized by the functional group R-C(=O)-H. Aldehydes are ionizable in water and exhibit excess aquatic toxicity in addition to narcosis. **Polyaldehydes** are more toxic than monoaldehydes to aquatic organisms and **acrylic/vinyl/allylic aldehydes**, e.g., acrolein, are more toxic than polyaldehydes. Vinyl/allylic/acrylic aldehydes are a class of organic compounds characterized by both the aldehyde, R-C(=O)-H, and vinyl, H_2C=C-R, or allylic, R-C=C-R, functional groups. Allylic and vinyl aldehydes, e.g., acrolein, C=CC(=O), exhibit excess toxicity.

It is assumed that aldehydes need to be absorbed to be toxic, therefore, aldehydes with MW >1000 will be excluded from this category. Acute toxicity for aldehydes is known to be limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of >6.0, aldehydes show no effects at saturation during 96-h exposures to fish. Aldehydes which are solids at room temperature may show no toxicity at saturation at lower K_{ow} values depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be observed at saturation. For solids, the no effects at saturation has to be determined on a case-by-case basis. There are no measured upper K_{ow} limits for chronic toxicity at this time, but it may not be much above a log K_{ow} = 8. Future testing will determine K_{ow} limits.

Hazard Concerns: The toxicity for aldehydes has been determined through SAR Analysis:

SARs for **monoaldehydes**:

log fish 96-h LC50 (moles/L) = -0.449 log K_{ow} -3.314
where n=54, R^2=0.53, CLOGP<6, MW<1000;

log daphnid 48-h LC50 (millimoles/L) = -0.059 -0.608 log K_{ow}
where n=5, R^2=1.0, CLOGP<6, MW<1000;

log green algal 96-h EC50 (mmol/L) = 0.994 -0.812 log K_{ow} (CLOGP)
where n=2, R^2=1.0, CLOGP<6.4, MW<1000;

log fish ChV (millimoles/L) = -0.810 -0.680 log K_{ow} (CLOGP)
where n=3, R^2=0.97, CLOGP<8, MW<1000;

log daphnid ChV (millimoles/L) = -1.090 -0.576 log K_{ow} (CLOGP)
where n=2, R^2=1.0, CLOGP<8, MW<1000; and

log algal ChV (mmol/L) = 0.053 -0.644 log K_{ow} (CLOGP)
where n=5, R^2=0.99, CLOGP<8, MW<1000.

SARs for **polyaldehydes**:

log fish 96-h LC50 (millimoles/L) = -1.176 -0.371 log K_{ow} (CLOGP)
where n=2, R^2=1.0, CLOGP<6, MW<1000;

log fish 96-h LC50 (millimoles/L) = -1.021 -0.396 log K_{ow} (SRC)
where n=2, R^2=1.0, SRC<6, MW<1000;

log daphnid 48-h LC50 (mmol/L) = -1.059 -0.440 log K_{ow} (CLOGP)
where n=2, R^2=1.0, CLOGP<6, MW<1000;

log daphnid 48-h LC50 (mmol/L) = -0.875 -0.471 log K_{ow} (SRC)
where n=2, R^2=1.0, SRC<6, MW<1000;

log green algal 96-h EC50 (mmol/L)= -1.772 -0.364 log K_{ow} (CLOGP)
where n=3, R^2=0.99, CLOGP<6.4, MW<1000;

log green algal 96-h EC50 (mmol/L)= -1.620 -0.388 log K_{ow} (SRC)
where n=3, R^2=0.99, CLOGP<6.4, MW<1000;

log fish ChV (millimoles/L) = -2.298 -0.488 log K_{ow} (CLOGP)
where n=2, R^2=1.0, CLOGP<8, MW<1000;

log fish ChV (millimoles/L) = -2.092 -0.513 log K_{ow} (SRC)
where n=2, R^2=1.0, CLOGP<8, MW<1000;

log daphnid ChV (millimoles/L) = -1.798 -0.488 log K_{ow} (CLOGP)
where n=2, R^2=1.0, CLOGP<8, MW<1000;

log daphnid ChV (millimoles/L) = -1.592 -0.513 log K_{ow} (SRC)
where n=2, R^2=1.0, CLOGP<8, MW<1000;

log algal ChV (millimoles/L) = -2.313 -0.348 log K_{ow} (CLOGP)
where n=2, R^2=1.0, CLOGP<8, MW<1000; and

log algal ChV (millimoles/L) = -2.166 -0.367 log K_{ow} (SRC)
where n=2, R^2=1.0, CLOGP<8, MW<1000

SARs for **vinyl/allylic/acrylic aldehydes**:

log fish 96-h LC50 (mmoles/L) = -3.502 +0.017 log K_{ow} (CLOGP)
where n=3, R^2=0.25, CLOGP<6, MW<1000; and

log fish ChV (millimoles/L) = -4.377 -0.228 log K_{ow} (CLOGP)
where n=2, R^2=1.0, CLOGP<8, MW<1000.

Environmental Fate:

Boundaries: MW <1000. Log K_{ow} <6.0 for acute toxicity to fish and aquatic invertebrates; log K_{ow} <6.4 for toxicity to green algae as a 96-h EC50; and log K_{ow} assumed to be <8.0 for chronic toxicity to aquatic organisms, but could be higher.

General Testing Strategy:

I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (CFR §797.1400) and daphnids (CFR §797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; and solvent can be used to assist the aldehyde to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the aldehyde beyond its aqueous solubility limit. Stock solutions in water should be adjusted to pH near 7.0.

The algal toxicity testing (CFR §797.1050), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; and solvent can be used to assist the aldehyde to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the aldehyde beyond its aqueous solubility limit. Stock solutions in water should be adjusted to pH near 7.0.

If there is no significant risk from the aldehyde after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation	40 CFR 796.3100
Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

If there is no significant risk from the aldehyde after the results of biodegradation testing have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 3.

Tier 3. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (CFR §797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because the 7-d ELS toxicity test may underestimate chronic toxicity measured by the 28-d ELS toxicity test when the Chronic Values are compared. Stock solutions in water should be adjusted to pH near 7.0.

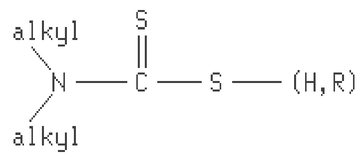
Daphnid chronic toxicity testing (CFR §797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because the fish 7-d ELS toxicity test may underestimate chronic toxicity measured by the fish 28-d ELS toxicity test when the chronic values are compared.

II. <u>Release to Terrestrial Ecosystems</u>: The <u>terrestrial</u> base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

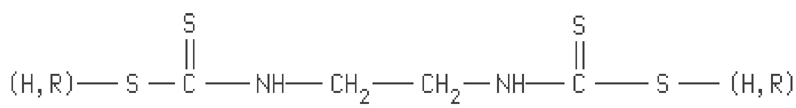
July, 1996

Category: Aliphatic Amines Environmental Toxicity

This category includes primary amines, secondary amines and tertiary amines; or monoalkyl amines, dialkly amines and trialkyl amines, respectively. This group includes alkanes, alkenes and alkynes; substitutions on carbon (alkyl) chains may include but not be limited to halogens and hydroxyls; insertions in alkyl chain may include but not be limited to ethoxys, propoxys, ethers, sulfides, disulfides and polysulfides; amine oxides are also included in this category; fatty polyamines (e.g., diamines, triamines, tetraamines, pentamines, etc) are also included; amines may either be un-ionized (free) or ionized; and strong ion pairs may also be included.



N,N-dialkyldithiocarbamate



ethylenebisdithiocarbamate

Hazard Concerns: Members of this category can be highly toxic to all groups of freshwater organisms (i.e., fish, aquatic invertebrates and green algae). Toxicity is related to the length of the hydrophobic carbon chains: the longer (or greater the number of carbons) the chain the more toxic to aquatic organisms when the number of amines is constant; and the greater the number of amines, the greater the toxicity given a constant carbon chain length. Small aliphatic amines are more toxic to algae than fish and invertebrates; higher molecular weight amines are equally toxic to all aquatic organisms. Small aliphatic amines which are un-ionized are more toxic to fish than when they are ionized; toxicity to algae appears to be unaffected by ionization. Strong ion pairs are generally much less toxic to fish and invertebrates because of solubility limitations, but remain highly toxic to green algae. The toxicity of each amine will be predicted using structure-activity relationships (SARs) and analogs contained in a generic standard environmental hazard review for aliphatic amines.

Boundaries: There are no lower boundaries and the upper boundary is unknown at this time. It is known that a C13-NH3 Cl is still toxic to fish at less than 1 mg/L. An upper boundary for carbon chain length will probably be about 20 carbons but more information is needed at this time. Generally, members of this category will have molecular weights less than 1000.

General Testing Strategy

Tier 1. The base set of environmental toxicity tests in clean dilution water and two fish acute toxicity tests done in the presence of humic acid (i.e., TOC) will be recommended. These test will be done under static methods with nominal concentrations. Smaller amines (e.g., Schiff bases) are expected to demonstrate less mitigation by humic acid (larger log P, greater mitigation; increase log P correlates to increased MW). If hydrolysis 1/2 life is less than one hour, test the hydrolysis product; if it is greater than one hour, test parent material.

Tier 2. If TOC significantly reduces the toxicity to water column species, then toxicity testing for toxicity to benthic organisms (i.e., organisms that ingest sediment) will be recommended; however, if TOC does not significantly reduce the toxicity to water column species, then chronic toxicity with fish and aquatic invertebrates will be recommended as well as aerobic biodegradation testing.

Aerobic biodegradability can be determined using one of the following test guidelines, listed in approximate order of preference:

Aerobic aquatic biodegradation	40 CFR 796.3100
Modified Sturm test	40 CFR 796.3260
Closed bottle test	40 CFR 796.3200
Modified OECD screening test	40 CFR 796.3240
Modified MITI test (I)	40 CFR 796.3220
Modified AFNOR test	40 CFR 796.3180

September 1988; revised November 1995.

Category: <u>Alkoxysilanes</u>

Human Health
Environmental Toxicity

Definition. Any molecular structure containing one or more of the following reactive groups is considered to be a member of the category.

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 |  |
-C-O-Si-
 |  |
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The "typical" new chemical of concern is a polymer with a substantial fraction of species with molecular weights <1000 and pendant trimethoxy- or triethoxysilane groups.

Hazard Concerns.

Health - Concern for lung toxicity from inhalation of vapors or aerosols is based on data for a number of low-molecular-weight alkoxysilanes. Trimethoxysilane (TMS) is clearly the most toxic member of the class causing irreversible lung effects at low doses, but the Agency does not consider it appropriate to use TMS as a regulatory benchmark for all alkoxysilanes.

For trimethoxysilane monomers and polymers with a low trimethoxysilyl equivalent weight, a NOAEL of 10 ppm (about 11 mg/kg/day) based on a 90-day study with vinyltrimethoxysilane in monkeys is deemed an appropriate generic benchmark.

Alkoxysilanes in which the alkyl substituent is **not** a methyl group do not appear to be as toxic as methoxysilanes. The New Chemicals Program currently uses a generic benchmark NOAEL of 75 mg/kg/day, based on a 90-day inhalation study with tri(isopropenoxy)silane, for alkoxysilanes other than methoxysilanes.

Ecotoxicity - Alkoxysilanes are highly toxic to algae and moderately toxic to aquatic invertebrates. For example, the daphnid 48-hr LC_{50} for dimethyldiethoxysilane is 1.25 mg/L, and the 15-day algal $EC_{95's}$ for vinyltriethoxysilane, tetraethoxy-silane, and trifluoropropenyl(methyl)diethoxysilane are all approximately 10 μg/L.

Boundaries. Methoxy- and ethoxysilanes are presumed not to pose a hazard under any conditions if the equivalent weight is $\geq$5,000 and no more than 25% of species have molecular weights less than 1,000 and no more than 10% of species have molecular weights less than 500. For alkoxysilanes with alkyl substituents larger than propyl groups, the equivalent weight cutoff is 1,000. The degree of concern depends on the relative abundance of lower molecular weight species, but there is no molecular weight threshold above which there would be no concern.

To better define the boundaries of the category, EPA seeks testing on a limited number of alkoxysilanes that focuses on (1) the relationship between molecular weight (or alkoxysilyl equivalent weight) and inhalation toxicity and (2) the importance of increasing alkoxy chain length in limiting toxicity.

General Testing Strategy

The Agency recommends the following testing as appropriate to address health and environmental toxicity concerns for this category:

1. 90-day subchronic test in rodents by the inhalation route (40 CFR 798.2650).

2. Hydrolysis testing (40 CFR 796.3500). If $t_{1/2}$ is less than one hour, base set ecotoxicity testing (see "3," below) is conducted with the hydrolysis products only. If $t_{1/2}$ is greater than one hour, base set ecotoxicity testing is conducted with the parent material; the PMN submitter has the option of also testing with the hydrolysis products.

3. Base-set ecotoxicity testing to include fish (40 CFR 797.1400) using the static method, daphnids (40 CFR 797.1300) using the static method and algae (40 CFR 797.1050) using the static method, all nominal concentrations. Direct dilution of the test alkoxysilane and organisms is added within 10 minutes. The static-renewal method is used for fish and daphnid test, plus an additional fish test using aged stock solution.

   Results of the acute ecotoxicity testing may trigger chronic fish (40 CFR 797.1600) and daphnid (40 CFR 797.1350) testing.

4. Physical-chemical or environmental fate testing including, as appropriate, melting point (40 CFR 796.1300) or boiling point (40 CFR 796.1220), water solubility (40 CFR 796.1840 or 796.1860), log K_{ow} (40 CFR 796.1550, 796.1570 or 796.1720), vapor pressure (40 CFR 796.1950), direct photolysis and indirect photolysis (40 CFR 796.3765). Need for water solubility, log K_{ow}, and photolysis testing determined by outcome of above hydrolysis testing.

September, 1988; revised June, 1994

Category: <u>Aluminum Compounds</u>

Risk Management Statement. Greatest concern is for soluble forms of aluminum (Al). If water solubility is greater than 1 part per billion (1 ppb), the Agency will prohibit releases of the PMN substance to water pending the submission of environmental toxicity testing.

Definition. This category includes inorganic salts of Al, complexes between Al and organic acids or chelates of Al by polyanionic monomers, and organoAl compounds, i.e., Al covalently-bonded with carbon. For example, some inorganic Al salts include: Al hydroxide, Al chloride, Al fluoride, Al nitrate, Al phosphate, and Al sulfate. Not included in this category are dyes complexed with Al (see dye categories addressed elsewhere within this "TSCA New Chemicals Program Chemical Categories" document).

Hazard Concerns. <u>Soluble salts of Al</u> are known to be highly toxic to green algae and moderately toxic to fish and aquatic invertebrates at pH values between 6.5 to 9.0 and in terms of soluble Al in mg Al/L. Toxicity information are available for Al chloride, Al sulfate, and Na aluminate. The Office of Water (USEPA, 1988, EPA440/5-86-008) cited Seipt et al. (1984, Water Air Soil Pollut. 23:81-95) who concluded that "the simple hydroxides ($Al(OH)^{2+}$ and $Al(OH)_2^+$) are regarded as the most dangerous forms while organically bound Al and polymeric forms are less toxic or essentially harmless." The Office of Water (USEPA, 1988) also concluded that solutions of Al in water approach chemical equilibrium rather slowly and that Al can form strong complexes with fulvic and humic acids.

The <u>toxicity profile for soluble Al salts</u>, listed below, is based on (1) available measured (M) toxicity data, (2) mg Al/L (ppm Al), (3) pH between 6.5 and 9.0, and (4) moderate hardness (about 150.0 mg/L as $CaCO_3$).

fish (FHM) 96-h LC50	=	35.0	M pH7.3 H220
fish (RT) 96-h LC50	=	8.6	M pH7.5 H47
fish (RT) 96-h LC50	=	7.4	M pH6.6 H47
fish (RT) 96-h LC50	=	14.6	M pH7.3 H47
mean RT 96-h LC50	=	10.0	P n3
fish (BT) 96-h LC50	=	3.6	M pH6.5 H?
mean fish 96-h LC50	=	11.0	P n3

daphnid (Cd) 48-h LC50	=	1.9	M pH7.4 H50
daphnid (Cd) 48-h LC50	=	3.7	M pH7.7 H47
mean Cd 48-h LC50	=	2.7	P n2
daphnid (Dm) 48-h LC50	=	3.9	M pH7.0 H45
daphnid (Dm) 48-h LC50	=	38.0	M pH7.1 H220
mean Dm 48-h LC50	=	12.0	P n2
mean daphnid 48-h LC50	=	5.7	P n2

OW FW Acute WQC = 1.5

green algal 96-h EC50	=	0.570 M pH7.6 H15
green algal 96-h EC50	=	0.460 M pH8.2 H15
mean algal 96-h EC50	=	0.510 P n2
fish (FHM) ChV	=	3.3 M pH7.7 H220
fish (FHM) ACR	=	11.0 M
daphnid (Dm) ChV	=	0.742 M pH8.3 H220
daphnid (Dm) ChV	=	0.320 M pH7.7 H45
mean Dm ChV	=	0.490 P n2
Dm ACR	=	24.0 M
daphnid (Cd) ChV	=	1.9 M pH7.2 H50
Cd ACR	=	1.4 M
mean daphnid ChV	=	0.970 P n2
mean daphnid ACR	=	5.9 M
OW FW Chronic WQC	=	0.087
algal ChV	=	0.100 P EC50÷4

Biological Fate

Fish (BT-eyed embryo) 30-d BCF (wb) = 50.0 M pH7.2 H242
Fish (BT-fry) 30-d BCF (wb) = 136.0 M pH7.2 H242
mean fish BCF = 93.0 P n2

The toxicity profile for soluble inorganic complexes of Al can be predicted via MW adjustment of the toxicity for Al to the toxicity of the complex.

Ca Al hydroxy phosphites [141 728-04-3]
$Ca_x\ Al_2(OH)_{2\,(x+3-y)}\ (HPO_3)_y \cdot mH_2O$ with x = 2 to 12, (2x+5)÷2 >y>0, and m = 0 to 12; typical composition = 31% Ca, 9.5% Al, & 8.0% P; solid with mp >250 °C (dec); S = 680 mg/L; pH 11.5;

Effect	Concentration (mg/L) Complex	Al	Notes
fish 96-h LC50	120.0	11.0	P
fish 96-h LC50	409.0	6.0	M
daphnid 48-h LC50	60.0	5.7	P
daphnid 48-h LC50	24.0	nm	M
green algal 96-h EC50	5.4	0.510	P
fish ChV	35.0	3.3	P

daphnid ChV	10.0	0.970 P
algal ChV	1.0	0.100 P

Na Al fluoride [15 096-52-3]
sodium fluoaluminate; sodium fluoride aluminum; cryolite; kryolith; M12,2673; $Na_3 Al F_6$; MW210; composition: 13% Al; solid with mp 1000 °C; S = 610 mg/L with pH 6.2; used as an insecticide since 1929;

Effect	Concentration (mg/L)		
	Complex	Al	Notes
fish 96-h LC50	85.0	11.0	P
fish 96-h LC50	21.0	2.8	M
daphnid 48-h LC50	44.0	5.7	P
green algal 96-h EC50	3.9	0.510	P
fish ChV	25.0	3.3	P
daphnid ChV	7.5	0.970	P
algal ChV	0.770	0.100	P

The toxicity profile for chelates of Al with polyanionic monomers can be predicted via MW adjustment of the toxicity for Al to the toxicity of the chelate.

The toxicity profile for organoAl compounds are developed for only the hydrolysis product(s) of Al. OrganoAl compounds are unstable in air and water. MethylAl and ethylAl are pyrophoric and dodecylAl slowly hydrolyses in water.

Boundaries. The toxicity of Al compounds depends on the their water solubility, the bioavailability of Al, and their stability. The most important property determining the toxicity of Al compounds is water solubility. Water solubility cannot be predicted accurately and has to be measured. Molecular weight (MW) is only important when Al complexes are water soluble and stable. Stable complexes of Al with MWs > 1000 are not expected to be absorbed by aquatic organisms and Al is not expected to be bioavailable even if they are water soluble. Therefore, only unstable Al compounds with MWs < 1000 are expected to be toxic.

General Testing Strategy

Tier 1. Fate testing. Physical state (OPPTS 830.6303) and corresponding property, i.e., melting point-melting point range (OPPTS 830.7200) or boiling point-boiling point range (OPPTS 830.7220), water solubility (OPPTS 830.7840 or 7860), octanol/water partition coefficient (K_{ow}) (OPPTS 830.7550 or 7570), and vapor pressure (OPPTS 830.7950); and/or

Acute environmental toxicity testing. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures: fish acute toxicity, daphnid acute toxicity, and green algal toxicity. The acute toxicity tests for fish (40 CFR §797.1400 or OPPTS 850.1075) and daphnids (40 CFR §797.1300 or OPPTS 850.1010) will be done using the static method; effective concentrations will be based on 100% active ingredients (ai) and nominal concentrations; the total organic carbon (TOC) concentration of dilution water in the control must be less than 2.0 mg TOC/L; TOC must be measured in the control just prior to the start of the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can not be used; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$.

The algal toxicity testing (40 CFR §797.1050 or OPPTS 850.5400), should be done with the static method; effective concentrations based on 100% ai and nominal concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with no more than 0.300 mg/L EDTA as a final concentration; the TOC of the test/growth medium should be less than 2.0 mg TOC/L; TOC should be measured just prior to the start of the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; and solvent can not used; .

In addition fish-toxicity-mitigation testing (OPPTS 850.1085) with known amounts of humic acid (HA) added to dilution water, i.e., 20 mg HA/L and 10 mg HA/L, will be recommended.

If there is no significant risk from the Al compound after the results of tier one testing set have been integrated into the risk assessment, then no further testing will be recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Fate testing. Aerobic biodegradation, i.e., ready biodegradation (OPPTS 835.3110) or sealed-vessel test (OPPTS 835.3120); and/or

Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR §797.1600 or OPPTS 850.1400), with the flow-through method; effective concentrations based on 100% ai and mean measured concentrations of soluble Al; statistical analysis of effective concentrations at days 7, 14, 21, and 28; the TOC of dilution water in the control should be less than 2.0 mg TOC/L; TOC should be measured in the controls just prior to and during the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can not be used; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$; and

Daphnid chronic toxicity testing (40 CFR §797.1330 or OPPTS 850.1300), with the flow-through method; effective concentrations based on 100% ai and mean measured concentrations of soluble Al; statistical analysis of effective concentrations at days 7, 14, and 21; the TOC of dilution water in the control should not exceed 2.0 mg TOC/L; TOC must be measured in the controls just prior to and during the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can not be used; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$.

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests will be recommended for terrestrial exposures. The terrestrial base set includes: the early seeding growth test (40 CFR 797.2800 or OPPTS 850.4230), the earthworm toxicity test (40 CFR.795.150 or OPPTS 850.6200), the soil microbial community bioassay (40 CFR 797.3700 or OPPTS 850.5100), and the avian acute oral toxicity test (40 CFR 797.2175 or OPPTS 850.2100). Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test (OPPTS 850.xxxx), the plant uptake test (40 CFR 797.2850 or OPPTS 850.4800), and the avian reproduction test (OPPTS 850.2300).

Abbreviations.

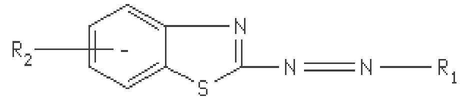
ACR10 = acute-to-chronic ratio = 10;
ai = active ingredients;
BCF = bioconcentration factor;
BT = brook trout;
Cd = *Ceriodaphnia*;
ChV = Chronic value;
Dm = *Daphnia magna*;
EC = effective concentration;
FHM = fathead minnow;
FT = flow-through method;
FW = fresh water;
H = hardness in mg $CaCO_3$/L;
H? = hardness unknown;
LOEC = lowest-observed-effect concentration;
M = measured concentrations;
n# = sample size used in calculation of the mean;
nm = not measured;
NOEC = no-observed-effect concentration;
OW = Office of Water;
P = predicted;
RT = rainbow trout;
S = static method;
SAR = structure activity relationship;
SR24 = static renewal method with renewals every 24 h;
TOC = total organic carbon;
wb = whole body;
WQC = water quality criterion;

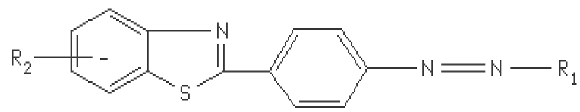
August, 1997

Category: <u>Aminobenzothiazole Azo Dyes</u>

Human Health
Environmental Toxicity

Definition. Any disperse azo dye containing the substructure 2-aminobenzothiazole or 2-(p-amino)phenylbenzothiazole, or phenyl ring-substituted derivatives of the same, is considered to be a member of the category.





Hazard Concerns. There are oncogenicity/mutagenicity concerns for intact aminobenzothiazole azo dyes by analogy to dimethyl aminostyryl benzothiazole and Butter Yellow-type dyes, such as 4-ethyl-N,N-diethylaminoazobenzene. In addition, there are liver and thyroid concerns for reduction products by analogy to 2-aminothiazole, and neuro-toxicity concerns by analogy to chlorinated 2-aminobenzothiazole. Ecotoxicity concerns are generally chronic concerns only and are based on QSAR predictions for neutral organic compounds. Neutral organic compounds are an established ecotoxicity category, of which these dyes are part of the disperse dye subclass.

Boundaries. The boundaries are not strictly defined. For a typical member of the category, R_1 = N- and/or ring substituted p-aminophenyl groups, and R_2 = halogens or nitro groups.

<u>General Testing Strategy</u>

The New Chemicals Program considers the following tests to be the most appropriate for aminobenzothiazole azo dyes found to pose an unreasonable risk:

- <u>In</u> <u>vivo</u> mouse micronucleus assay in bone marrow by the i.p. route (40 CFR 798.5395).

- 90-day subchronic toxicity test in rats by the oral route, with special attention to the thyroid and liver (40 CFR 798.2650).

- Fish early life stage test (40 CFR 797.1600). Chronic daphnid test (40 CFR 797.1350). Algae toxicity test (40 CFR 797.1050).

- If the mouse micronucleus assay is positive, further characterization of the potential cancer risk may be recommended: 2-year cancer bioassay by the oral route in 2 species of rodents (40 CFR 798.3260).

Potentially significant ecotoxicity risk, as well as human health risks, resulting from releases to water **ONLY**, may be addressed by environmental fate testing prior to the chronic ecotoxicity and human health testing. The results of the environmental fate testing may preclude the need for further testing.

- Jar test to determine the settling rate and extent of removal of suspended solids from solution (draft protocol available).

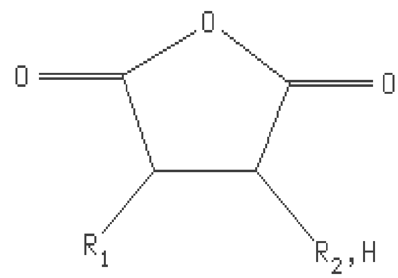
If the results of the jar test do not mitigate the health and/or ecotoxicity concerns, further characterization of the environmental fate of the dye may be recommended.

- Coupled units test (40 CFR 796.3300).

January, 1992.

Category: <u>Anhydrides, Carboxylic Acid</u> Human Health

Definition. Any molecular structure containing one or more carboxylic acid anhydride groups is considered to be a member of the category for new chemical purposes. Members of the class include new carboxylic acid anhydrides as well as new oligomers, polymers, prepolymers, or reaction products of existing carboxylic acid anhydrides. As illustrated below, a typical new chemical carboxylic acid anhydride of concern is a polymer or oligomer containing a monomer such as maleic anhydride.



Hazard Concerns. Carboxylic acid anhydrides are of concern for potential pulmonary sensitization based on data for phthalic, trimellitic, isopropylidene bis(phthalic), and sulfonyl bis(phthalic) anhydrides. Carboxylic acid anhydrides are also of concern for potential developmental or reproductive toxicity based on data for maleic, succinic, and phthalic anhydrides.

Boundaries. Structures with a carboxylic acid anhydride equivalent weight of ≥5,000 are presumed not to pose a hazard under any conditions. Typically, concerns for health effects are confined to those species with molecular weights <1,000.

The new chemical program has thus far been concerned only with those carboxylic acid anhydrides with potentially significant inhalation exposure, and has pursued developmental toxicity only for low molecular weight (<500) carboxylic acid anhydrides which are thought to have a significant potential for systemic uptake via the lung. For pulmonary sensitization, extensive systemic uptake may not be necessary for a biological response and we have therefore sought to regulate some oligomeric or polymeric carboxylic acid anhydrides only for that effect.

<u>General Testing Strategy</u>

The following tests are usually prescribed for carboxylic acid anhydrides found to pose a potentially unreasonable risk:

- Pulmonary sensitization by either the method of Karol (Toxicol. Appl. Pharmacol. 68:229-241, 1983), or an equivalent method.
- Oral developmental toxicity study in two species (40 CFR §798.4900).

May, 1991

Category: Anilines Environmental Toxicity

This category includes all anilines, both monoanilines and polyanilines. It is assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will be excluded from this category. Acute toxicity for anilines which are liquids at room temperature is known to be limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of => 7.38, anilines show no effects at saturation during 96-h exposures (Veith and Broderius (1987). Anilines which are solids at room temperature may show no toxicity at saturation at lower Kow values depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be observed at saturation. For solids, the no effects at saturation has to be determined on a case-by-case basis. There are no known Kow limits for chronic toxicity at this time, but it may not be much above a log K_{ow} = 8 for liquid anilines. Future testing will determine this K_{ow} limit.

Hazard Concerns. The acute toxicity for anilines has been determined through SAR Analysis:

fish 96-h LC50 (Veith and Broderius 1987);
fish 14-d LC50 (Deneer et al 1987);
fish 14-d LC50 (Hermens et al 1984);
daphnids 48-h LC100 (Nendza and Seydel 1988a and 1988b); and
green algal 96-h EC50 (Nendza and Seydel 1988a and 1988b).;

The neutral organic SARs can be used to predict green algal 96-h EC50.

Aromatic diamines (i.e., two amines on one benzene) and dinitroanilines are known to be more toxic than predicted by these SARs.

Members of this category exhibit toxicity ranging from low toxicity (i.e., > 100 mg/L) to high toxicity (i.e., < 1 mg/L) depending on their K_{ow}, MW and substitutions (e.g., dinitroanilines).

Environmental Fate. Some recent studies have shown that certain anilines are subject to rapid direct and indirect photolysis under environmentally realistic conditions (Leifer 1990).

Boundaries. There are no known lower boundaries. The upper boundaries will be based on K_{ow} and MW. Acute toxicity expected with log K_{ow} < 7.38; no effects at saturation during 96-h exposures when log K_{ow} >= 7.38. Chronic toxicity has no known upper bound for log K_{ow}, but it is probably near 8. MW will be < 1000. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log K_{ow} is >= 7.38, chronic toxicity testing with fish and daphnids will be recommended.

General Testing Strategy.

I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR 797.1400) and daphnids (40 CFR 797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should equal the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

The algal toxicity testing (40 CFR 797.1050), should be done with static methods; measured concentrations.; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis equal to the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

If there is no significant risk from the PMN after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Direct and Indirect Photolysis Screening Test (40 CFR 796.3765). If $t½ \leq 2$ days, go to Tier 3; if $t½ > 2$ days, go to Tier 4.

Tier 3a. If $t½ \leq 2$ days and photolysis products are known and/or identified, then assess photolysis products for environmental hazards.

Tier 3b. If $t½ \leq 2$ days and photolysis products are not known and/or identifiable, then prepare a stock solution of PMN using the standard humic-containing solution described in the direct and indirect photolysis screening test [40.796.3765 (b)(2) and (c)(2)], expose to sunlight for at least 6 half-lives (t½), and test photolysis products for toxicity with most sensitive species from environmental base set. For example, the most sensitive species from the environmental base set has an EC50 value = 2.0 mg PMN/L (based on 100% active ingredients [AI]), therefore, prepare a 5.0 mg PMN per liter stock solution based on 100% AI using the standard humic-containing solution. This stock solution is exposed to sunlight for at least 6 half-lives to ensure that all of the PMN has been photolyzed, and then this stock solution is used to retest the most sensitive aquatic species to determine if the photolysis products of the PMN are more or less toxic that the PMN.

Tier 4. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR 797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because Van Leeuwen et al (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen);

Daphnid chronic toxicity testing (40 CFR 797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because Van Leeuwen et al (1990) have demonstrated that the fish 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the fish 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen).

Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation	40 CFR 796.3100
Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

II. <u>Release to Terrestrial Ecosystems</u>: The <u>terrestrial</u> base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

References.

Deneer JW, Sinnige TL, Seinen W and Hermens JLM. 1987. Quantitative structure-activity relationships for the toxicity and bioconcentration factor of nitrobenzene derivatives towards the guppy (Poecilia reticulata). Aquatic Toxicology 10:115-129.

Hermens J, Leeuwangh P, and Musch A. 1984. Quantitative structure-activity relationships and mixture toxicity studies of chloro- and alkylanilines at an acute lethal toxicity level to the guppy, Poecilia reticulata. Ecotoxicology and Environmental Safety 8:388-394.

Leifer A. 1990 (14 Dec). Review of Section 5 test data for o-phenylenediamine, m-phenyldiamine, and p-phenylenediamine. Memorandum. Washington, DC: Exposure Assessment Branch, Exposure Evaluation Division (TS-798), Office of Toxic Substances, United Stated Environmental Protection Agency, 401 M St, SW, 20460-0001.

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Nendza M and Seydel JK. 1988b. Quantitative structure-activity relationships for ecotoxicologically relevant biotest systems and chemicals. Chemosphere 17:1585-1602.

Van Leeuwen CJ, Adema DMM, and Hermens J. 1990. Quantitative structure-activity relationships for fish early life stage toxicity. Aquatic Toxicology 16:321-334.

Veith GD and Broderius SJ. 1987. Structure-toxicity relationships for industrial chemicals causing type (II) narcosis syndrome. In Kaiser KLE (ed), QSAR In Environmental Toxicology - II, p 385-391. Reidel Publishing Company.

May, 1991

Subcategory of Anilines: Dianilines

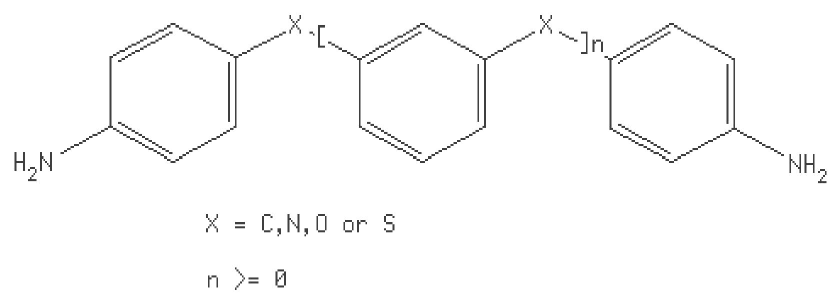
Human Health
Environmental Toxicity

Definition. A PMN must have the following minimum structural requirements to be considered a member of this category:

-it must have at least two phenyl rings with a bridging carbon, oxygen, nitrogen, or sulfur

-each terminal phenyl ring must have a primary amino group (or a group that can be readily metabolized to a primary amino group) either meta- or para- to the bridging atom

Compounds with one or more additional phenyl ring(s), with or without ring substituents, and one or more bridging atoms are also included in the category.



Minimum Structure for Dianiline Category

The compounds of greatest concern are those having X = C, N, or O and n = 0 or 1.

Hazard Concerns: Members of the class are considered to be potential carcinogens and mutagens by analogy to 4,4'-methylendianiline, 4,4'-methylene bis(o-toluidine), and 4,4'-oxydianiline. Class members are potential retinotoxic agents by analogy to 4,4'-methylenedianiline, 4,4'-oxydianiline, and the diaminodiphenyl alkane drugs and are also potential reproductive and systemic toxicants by analogy to 4,4'-methylenedianiline.

General Testing Strategy

The New Chemicals Program has considered the following toxicity tests to be the most appropriate for dianilines found to pose an unreasonable risk:

I. Exposure to Humans

- rat acute oral retinopathy screening study (protocol to be approved by EPA)

- pigmented rat 90-day subchronic toxicity study by the oral (40 CFR 798.2650) or inhalation (40 CFR 798.2450) route to include histopathological examination of the eyes and reproductive organs (eyes to be examined by both light and electron microscopy)

- 2-year carcinogenicity bioassay (40 CFR 798.3300) in rats and mice.

In the 90-day subchronic toxicity study, the company may opt to carry a group of animals at each dose level for a 90-day recovery period to determine whether potential retinopathy is reversible.

For some compounds in this class, short-term mutagenicity testing may be appropriate. When appropriate, specific testing will be determined by EPA mutagenicity assessors on a case by case basis by referral to "short question."

Where the general population is at a significant risk from drinking water exposure (via surface water releases) to PMN chemicals of this class, the following fate testing may be appropriate:

-direct and indirect photolysis 40 CFR 796.3765 and 796.3700

-aerobic aquatic biodegradation 40 CFR 796.3100

-see aniline category description for details

Results of the above fate tests may mitigate concern for drinking water exposure to PMN of this class. However, fate test results WILL NOT CHANGE AGENCY CONCERNS FOR OCCUPATIONAL EXPOSURE to PMNs of this category.

II. Release to Aquatic Ecosystems

Tier 1. Because of the above boundary conditions, and the need to assess human exposure as well as environmental toxicity, if there is insufficient knowledge about the water solubility of the dye, then it should be measured (40 CFR §796.1860). The fish and daphnid acute toxicity tests from the aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR §797.1400) and daphnids (40 CFR §797.1300) will be done using the flow-through method with measured concentrations, and effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations.

If there is no significant risk from the PMN after the results of the fish and daphnid acute toxicity tests have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Direct and Indirect Photolysis Screening Test (40 CFR 796.3765). If $t½ \leq 2$ days, go to Tier 3; if $t½ > 2$ days, go to Tier 4.

Tier 3a. If $t½ \leq 2$ days and photolysis products are known and/or identified, then assess photolysis products for environmental hazards.

Tier 3b. If $t½ \leq 2$ days and photolysis products are not known and/or identifiable, then prepare a stock solution of PMN using the standard humic-containing solution described in the direct and indirect photolysis screening test [40 CFR 796.3765 (b)(2) and (c)(2)], expose to sunlight for at least 6 half-lives (t½), and test photolysis products for toxicity with most sensitive species from environmental base set.

Tier 4. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR 797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; and statistical analysis of effective concentrations at days 7, 14, 21, and 28.

Daphnid chronic toxicity testing (40 CFR 797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21.

Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation	40 CFR 796.3100
Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

III. <u>Release to terrestrial Ecosystems</u>:

The <u>terrestrial</u> base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

References

American Dye Manufacturers Institute, Inc. (1974). "Dyes and the Environment: Reports on Selected Dyes and Their Effects," Vol. II, ADMI, New York.

Auer, C.M., Nabholz, J.V. and Baetcke, K.P. (1990). "Mode of Action and the Assessment of Chemical Hazards in the Presence of Limited Data: Use of Structure-Activity Relationships (SAR) under TSCA, Section 5," Environmental Health Perspectives, Vol. 87, pp. 183-197.

Little, L.W., and Lamb J.C., III (1972). "Acute Toxicity of 46 Selected Dyes to the Fathead Minnow, Pimephales promelas, "Final Report to the American Dye Manufacturers Institute, Inc., UNC Wastewater Research Center, Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina, Chapel Hill, NC.

Nabholz, J.V. (1990). "The OTS PMN ECOTOX Data Base: a Confidential Business Information (CBI) Collection of Environmental Toxicity Data from New Chemical Submissions Under Sec. 5," Unpublished, Environmental Effects Branch, Health and Environmental Review Division (TS-796), U. S. Environmental Protection Agency, Washington, DC.

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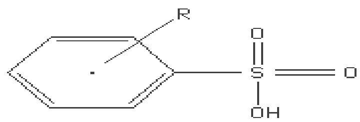
Tonogai, Y., Ito, Y., Iwaida, M., Tati, M., Ose, Y., and Sato, T. (1979). "Studies on the Toxicity of Coal-Tar Dyes. II. Examination of the Biological Reaction of Coal-Tar Dyes to Vital Body," The Journal of Toxicological Sciences, Vol. 4, pp. 211-219.

August 1991; revised January 1995; revised October 1995

Category: <u>Anionic Surfactants</u> Environmental Toxicity

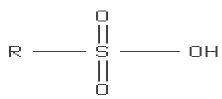
Definition. Any molecular structure with a net negative charge and having surfactant activity is a member of this category. The category includes for example, alkyl sulfonates, alkyl benzene sulfonates, alkyl silicic acids, alkyl phosphates, alkyl carboxylic acids, or combinations of these anionic groups, e.g., alkyl sulfonate with carboxylic acid substitutions.



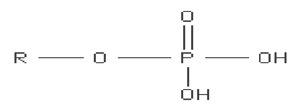
alkyl benzene sulfonate (LAS)

SOME EXAMPLES ARE:

R = straight chain alkyls



alkyl sulfonate



alkyl phosphate

Hazard Concerns. Anionic surfactants are toxic to a wide variety of aquatic organisms. Toxicity increases exponentially with increasing carbon chain length up to 16 carbons [for linear alkyl sulfonate (LAS) surfactants], and then decreases with additional carbons. At a chain length of 16 carbons, fish and daphnids are most sensitive, but at lower chain lengths green algae are more sensitive than fish and daphnids. There are a number of structure-activity relationships (SARs) to predict the toxicity of members of this category. Most are parabolic regression equations and others rely on nearest analog methodology.

Boundaries. There is no molecular weight boundary. Surfactants with molecular weights > 1000 are still toxic. Acute toxicity may be low, i.e., > 100 mg/L, if a strong cationic surfactant counterion and the anionic surfactant form a tight ion pair.

Testing. To address ecotoxicity concerns, base set acute aquatic toxicity testing (green algae: static method, daphnid and fish: flow-through method, all measured concentrations).

Tier 1. The <u>acute aquatic base set</u> of environmental toxicity tests will be recommended for aquatic exposures and the <u>terrestrial base set</u> of environmental toxicity tests (i.e., the early seeding growth test, the earthworm acute toxicity test and the soil microbial community bioassay) will be recommended for any terrestrial exposures.

Acute fish toxicity test	OPPTS 850.1075
Acute daphnid toxicity test	OPPTS 850.1010
Green algae toxicity test	OPPTS 850.5400
Early seedling growth test	OPPTS 850.4230
Earthworm acute toxicity test	OPPTS 850.6200
Soil microbial community bioassay	OPPTS 850.5100

Tier 2. If acute toxicity testing indicates a significant risk, then environmental fate testing in the form of aerobic biodegradation testing is recommended. Aerobic biodegradability can be determined using one of the following test guidelines, listed in approximate order of preference:

CO_2 evolution	OPPTS 835.3110
Closed bottle	OPPTS 835.3110
Modified OECD screening	OPPTS 835.3110
Modified MITI (I)	OPPTS 835.3110
DOC die-away	OPPTS 835.3110
Manometric respirometry	OPPTS 835.3110

Tier 3. In addition, if acute toxicity testing indicates a significant risk, then chronic aquatic toxicity testing with fish and aquatic invertebrates will be recommended.

Fish early life stage test	OPPTS 850.1400
Daphnid chronic toxicity testing	OPPTS 850.1300

September 1988, revised September, 1996

Category: Azides Environmental Toxicity

Azides are a class of chemicals consisting of both inorganic and organic compounds and characterized by the functional group N=N=N. Substitutions may be either metals or organic compounds, e.g., acetic acid and benzene. So far, only monomeric aromatic azide compounds have been submitted as PMNs. No aliphatic azides, e.g., alkyl azides, have been submitted as PMNs. Aliphatic azides may be too explosive to isolate, however, diazidoacetic acid ester is known to exist and has been tested in rats.

Hazard Concerns: It is assumed that azides have to be absorbed to be toxic, therefore, azides with MW >1000 will be excluded from this category. Acute toxicity for monomeric azides is assumed to be correlated and limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of >5.0, azides are assumed to show no effects at saturation during 96-hour exposures to fish. Organic azides which are solids at room temperature may show no toxicity at saturation at lower K_{ow} values depending on their melting point and/or their water solubility. For example, for organic azides, the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be occur at saturation. For solids, no effects at saturation has to be determined on a case-by-case basis. There are no measured upper K_{ow} limits for chronic toxicity at this time, but it may not be much above a log K_{ow} = 8. Future testing will determine K_{ow} limits.

The aquatic toxicity of organic azides has been determined through SAR Analysis:

log fish 96-h LC_{50} (millimoles/L) = -1.881 -0.124 log K_{ow}
where n=2, R^2=1.0, LOGKOW(SRC)<5, MW<1000;

The toxicity for inorganic azides has to be determined by integrating the toxicity of Na azide with the toxicity of any other inorganic element, e.g., Pb, with a MW adjustment for differences in toxicity between Na azide and the other inorganic element. Na azide [26628-22-8] has been tested by the USEPA ERL-Duluth: fathead minnow 96-h LC_{50} = 5.46 mg/L based on a flow-through method with 18 volume changes per day and nominal concentrations. The SAR for organic azides is based on (1) this toxicity value, (2) a calculated log K_{ow} value of -6.3 using SRC's LOGKOW, and (3) no acute effects to fish at saturation assumed to occur at a log K_{ow} $\geq$5.0 which is equivalent to a log fish 96-h LC_{50} = -2.5 in millimoles per liter. CLOGP has a missing fragment constant for the azide group.

Environmental Fate: Na azide is known to hydrolyze in water to form hydrazoic acid (or hydrogen azide, NH_3, [7782-79-8], MW43, M12,4815). Hydrogen azide is extremely explosive according to Merck. In addition, azides can be transformed to nitrenes by *uv* light.

Boundaries: MW <1000. Log K_{ow} <5.0 for acute toxicity to fish and aquatic invertebrates; log K_{ow} <6.4 for toxicity to green algae as a 96-h EC_{50}; and log K_{ow} assumed to be <8.0 for chronic toxicity to aquatic organisms, but could be higher.

<u>General Testing Strategy</u>:

I. <u>Release to Aquatic Ecosystems</u>:

Tier 1. The <u>aquatic</u> base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (OPPTS 850.1075) and daphnids (OPPTS 850.1010) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (ai) and mean measured concentrations; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; and solvent can be used to assist the aldehyde to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the test chemical significantly above its aqueous solubility limit.

The algal toxicity testing (OPPTS 850.5400), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (ai) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; and solvent can be used to assist the aldehyde to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the test chemical significantly above its aqueous solubility limit.

If there is no significant risk from the PMN chemical after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. <u>Aerobic biodegradability</u> according to either of the following test guidelines:

Ready Biodegradability	OPPTS 835.3110
Sealed Vessel CO2 Production Test	OPPTS 835.3120

If there is no significant risk from the PMN chemical after the results of biodegradation testing have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 3.

Tier 3. <u>Fish chronic toxicity testing</u>, i.e., fish early life stage (ELS) toxicity testing (OPPTS 850.1400), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN significantly above its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because the 7-d ELS toxicity test may underestimate chronic toxicity measured by the 28-d ELS toxicity test when the Chronic Values are compared.

Daphnid chronic toxicity testing (OPPTS 850.1300), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN significantly above its aqueous solubility limit; and the 7-d daphnid short-term chronic toxicity test cannot be substituted for the 21-d toxicity test because the daphnid 7-d short-term toxicity test may underestimate chronic toxicity measured by the 21-d toxicity test when the chronic values are compared.

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test [OPPTS 850.4230], the earthworm toxicity test [OPPTS 850.6200], and the soil microbial community bioassay [OPPTS 850.5100]) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

References:

L'Abbe, G. (1969). Decomposition and addition reactions of organic azides. Chemical Review, 69, 345-363.

Scriven, E.F. (Ed.). (1984). Azides and nitrenes: Reactivity and utility. pp.95-204. New York: Academic Press.

September 1996

Category: <u>Benzotriazoles</u> Environmental Toxicity

Definition. This category includes all benzotriazoles.

Hazard Concerns. The toxicity for benzotriazoles with -NH has been determined through SAR Analysis (Clements 1988). Benzotriazoles with -NH are known to be more toxic than neutral organic chemicals, and this excess toxicity decreases with increasing K_{ow}. The toxicity of benzotriazoles with aliphatic substitutions on the nitrogen are expected to act like neutral organic compounds. Other substitutions on the N, e.g., -SH, have to be evaluated on a case-by-case basis.

Members of this category exhibit toxicity ranging from low toxicity (i.e., > 100 mg/L) to high toxicity (i.e., < 1 mg/L) depending on their K_{ow}, MW, and melting point.

Boundaries. There are no known lower boundaries. The upper boundaries will be based on K_{ow}, MW, and melting point (mp). These compounds need to be absorbed to be toxic, therefore, compounds with MWs < 1000 are expected to cause toxicity, while compounds with MWs > 1000 are no expected to show toxicity at saturation.

Acute toxicity for benzotriazoles which are liquids at room temperature is known to be limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of 5.0, benzotriazoles show no effects at saturation during 96-h exposures (Clements 1988). Benzotriazoles which are solids at room temperature may show no toxicity at saturation at lower K_{ow} values depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no acute toxicity will be observed at saturation. For solids, the no-effects-at-saturation point for acute toxicity has to be determined on a case-by-case basis.

The K_{ow} limit for chronic toxicity is set at a log K_{ow} = 8 for liquid benzotriazoles. For solids, chronic toxicity testing will determine the K_{ow} limit.

Therefore, acute toxicity is expected when log K_{ow} =< 5.0 and MW < 1000; no effects at saturation during 96-h exposures are expected when log K_{ow} > 5.0 and MW < 1000. The upper boundary for chronic toxicity is 8.0. Only chronic toxicity is expected when log K_{ow} > 5.0 and < 8.0, and MW < 1000. Whenever MW > 1000, no effects are expected at saturation because it is assumed that benzotriazoles have to be absorbed to be toxic.

Aerobic biodegradation is expected to be the dominant route of transformation in the environment.

General Testing Strategy.

I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR §797.1400) and daphnids (40 CFR §797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested chemical; and solvent can be used to assist the chemical to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the chemical beyond its aqueous solubility limit.

The algal toxicity test (40 CFR §797.1050) should be done with the static method; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the chemical; and solvent can be used to assist the chemical to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the chemical beyond its aqueous solubility limit.

If there is no significant risk from the benzotriazole after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation	40 CFR 796.3100
Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

If there is no significant risk from the benzotriazole after the results of the aerobic biodegradation testing have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 3.

Tier 3. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR §797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit for the chemical; solvent can be used to assist the chemical to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the chemical beyond its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because Van Leeuwen et al (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen). Both anilines and benzotriazoles with -NH are more toxic than predicted based on narcosis alone, i.e., both benzotriazoles and anilines have excess toxicity due to a more specific mode(s) of toxic action. A seven day exposure may not allow enough time for this excess toxicity to be expressed either because of not enough exposure and/or not enough time for metabolic activation.

Daphnid chronic toxicity testing (40 CFR §797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the chemical; solvent can be used to assist the chemical to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the chemical above its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test (Van Leeuwen et al 1990).

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test, the avian acute oral toxicity test, and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, the avian reproductive toxicity test, and the soil microbial community bioassay. In addition, the fate test for Inherent Biodegradability in soil (40 CFR §796.3400) may be recommended.

References

Clements, RG (editor). 1988. Estimating toxicity of industrial chemicals to aquatic organisms using structure-activity relationships. EPA-560-6-88-001. Washington, DC: Environmental Effects Branch, Health and Environmental Review Division, Office of Toxic Substances (TS-796), United States Environmental Protection Agency. Available from the National Technical Information Service, Springfield, VA 22161, PB89-117592.

Van Leeuwen CJ, Adema DMM, and Hermens J. 1990. Quantitative structure-activity relationships for fish early life stage toxicity. Aquatic Toxicology 16:321-334.

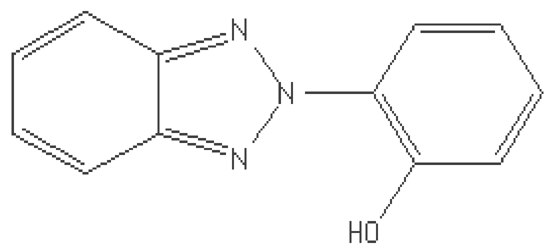
March, 1992

Category: <u>Benzotriazole-hindered phenols</u>

Human Health
Environmental Toxicity
(see "Phenols")

The predominant use of members of this category is as a UV light stabilizer in coating or plastic formulations.

Definition. Any molecular structure containing the following substructure is considered to be a member of the category.



<u>Note</u>: Health effects may vary depending on the nature of the ring substituents.

Hazard Concerns.

I. Health

<u>Systemic toxicity</u> based on 8(e) and PMN data on analogues. These data are generally consistent across compounds, with the following endpoints occurring in subacute, subchronic, and chronic oral feeding studies in rats and dogs in which doses ranged from 5 to 15,000 ppm.

Increased organ weights (liver and kidney, with associated histopathology at higher doses); hematological effects (decreased hemoglobin, packed cell volume, and erythrocytes); and immune system effects (weight changes in thymus, spleen, lymph nodes; decreased leukocytes). Generally, treatment-related effects are dose-related, increasing in frequency and severity with increasing dose. Males appear to be more sensitive than females, and similar toxic effects occur in both rats and dogs.

The lowest available **NOAEL** for systemic effects, from a 90-day rat study, is 5 ppm, or **0.25 mg/kg/day**.

<u>Reproductive toxicity</u> - Concern is also based on 8(e) and PMN data on analogues. As with

systemic toxiciy, the data are generally consistent, with the following endpoints occurring in subacute and subchronic oral feeding studies in rats and dogs in which doses ranged from 5 to 15,000 ppm.

Atrophy of the seminal vesicles, significant reduction in absolute and relative testes weight, significant reduction in absolute and relative prostate weight, and abnormal spermatogenesis. A subchronic dog study also provided evidence of female reproductive toxicity.

Generally, treatment-related effects are dose-related, increasing in both frequency and severity with increasing dose. Males appear to be more sensitive than females, and similar toxic effects occur in both rats and dogs.

The lowest **NOAEL** for reproductive toxicity, from a 90-day dog study, is **15 mg/kg/day**.

<u>Dermal sensitization</u> - Dermal sensitization test data were positive in 3/4 compounds tested. Two of the compounds showed strong sensitizing potential based on results obtained from maximization tests in which 70% and 90% of the treated guinea pigs became sensitized, respectively.

II. Environmental - The environmental concerns for the substances described in this category have already been described in the **Phenol** category.

Boundaries. Not enough is known about the structure-activity relationships of these compounds to set any boundaries on members of the category; compounds with both "small" and "large" substituents have shown effects, and the effects are generally consistent from compound to compound.

<u>General Testing Strategy</u>

I. Health

<u>Systemic Toxicity and Reproductive Toxicity</u>. A 90-day gavage study in rats with special attention to hematology; weight and histopathology of lymphoid organs (spleen, thymus, and bone marrow); cellularity of the bone marrow, thymus, and spleen; and histopathology of the liver, kidney, heart, and all endocrine glands for which weight changes are observed. Particular attention should be directed toward achieving satisfactory quality from fixation and embedding of the testes, following the recommendations of Russell et al. [Russell LD, Ettlin RA, Sinha Hikim AP, Clegg ED. 1990. Histological and histopathological evaluation of the testis. Cache River Press, Clearwater, FL].

A gavage study, as opposed to an oral feeding study, is recommended because decreased body weight gain, final body weight, and/or food consumption have been reported in some oral feeding studies with analogues.

If immunopathology and hematology in the 90-day study support the concern for adverse effects of the PMN substances on the immune system, then a further battery of tests, such as the NTP's Immunotoxicology Tier II Screening Panel, will be recommended.

Dermal Sensitization. Because dermal sensitization is not routinely pursued under TSCA 5(e) as a regulatory endpoint, testing is not recommended. A letter be sent to the PMN submitter expressing the Agency's belief that the compounds are likely to be dermal sensitizers and that protective measures should be taken for workers.

II. Environmental toxicity

If exposure to the aquatic environment demonstrates a potential risk, testing of the substances described in this category is the same as that prescribed for the **Phenols** category.

June, 1993.

Category: Boron Compounds | **Human Health**
Environmental Toxicity

Definition. This category includes borates, organoborates, borate esters, boron hydrides, boranes, and boroxines.

Human Health:

Hazard Concerns. Reproductive toxicity (males/females), blood toxicity, and neurotoxicity. The Agency has an **oral RfD for boron of 0.09 mg/kg/day** (uncertainty factor 100) based on the finding of testicular atrophy and spermatogenic arrest in dogs in a 2-yr feeding study (Weir and Fisher 1972, as summarized in IRIS 1995). [All toxicity information presented here are summarized in an assessment of various aqueous cleaner chemicals prepared in 1990 for the Office of Air and Radiation. Reproductive toxicity information also summarized in IRIS 1995.]

Reproductive Toxicity. The most significant effect seen in animals is reproductive toxicity (i.e., sterility in males and females, and testicular atrophy in males). A three-generation reproductive study in rats demonstrated sterility in males (lack of spermatozoa in atrophied testes) and females (decreased ovulation) after exposure to 58.5 mg boron/kg in the diet. NOAEL (rats) 17.5 mg boron/kg. Sterility was also found in males (at 50 or 100 mg boron/kg) in a serial mating adjunct to a 60-day feeding study; NOAEL (rats) 25 mg boron/kg.

Data from oral subchronic and chronic studies in rats, dogs, and mice also provide evidence that boron produces adverse effects on the male reproductive system. A statistically significant reduction in relative and absolute testes weights was seen in a 2-yr and a 90-day dietary study in male rats at 58.5 and 26.3 mg boron/kg, respectively. NOAEL's (rats) 17.5 and 8.8 mg boron/kg, respectively. In male rats, dietary exposure to 50 mg/kg boron resulted in a significant reduction in fertility, a significant reduction in epididymal weight, and a reduction in sperm number after 30 days of treatment. A significant reduction in testicular weight and further reduction in sperm occurred after 60 days of treatment. NOAEL (rats) 25 mg boron/kg. Similar results were observed in several drinking water studies in rats.

In male dogs, dietary exposure to 29.4 mg boron/kg for 2 yr resulted in severe testicular atrophy and spermatogenic arrest. NOAEL (dogs) 8.8 mg boron/kg. In male and female dogs, dietary exposure to 43.8 and 4.4 mg boron/kg for 90 days did not affect the female reproductive system, but produced decreased testes weights (statistically significant at 43.8 mg boron/kg). NOAEL (dogs) 0.4 mg boron/kg. In male mice, dietary exposure to 131 mg boron/kg for 103 wk (only dose tested) caused an increased incidence of testicular atrophy and interstitial hyperplasia.

Blood Toxicity. In a chronic feeding study in rats, packed cell volume and hemoglobin levels were significantly decreased in males and females at 58.5 mg boron/kg. NOAEL (rats) 17.5 mg boron/kg. In a subchronic drinking water study in rats, a significant decrease in plasma triglyceride levels was noted at 23.7 and 47.4 mg boron/kg (only doses tested). LOAEL (rats) 23.7 mg boron/kg. In a subchronic feeding study in dogs, 43.8 mg boron/kg but not 4.4 or 0.4

mg boron/kg produced decreased packed cell volumes and hemoglobin levels. NOAEL (dogs) 4.4 mg boron/kg. In a subchronic feeding study in mice, minimal to mild extramedullary hematopoiesis of the spleen was observed in all dosed groups (ca. 34, 68, 136, 272, or 544 mg boron/kg). LOAEL (mice) 34 mg boron/kg. There is also a case study in which an infant exposed to 43 mg boron/kg/day for 12 weeks developed anemia.

Neurotoxicity. Ingestion of borax by human infants results in neurotoxicity. Case reports of **nine infants** who were exposed by sucking pacifiers dipped in a borax-honey mixture document similar findings of neurological symptoms (not specified) and seizures. For seven infants, doses are reported as 2 to 3 g borax/wk for 4 to 10 wk (ca. 4 to 16 mg boron/kg/day). Serum boron levels measured in three of the seven infants were elevated. For the other two infants, doses are reported as 125 mg borax/kg over a 12-wk period and 9 g borax over a 5-wk period (ca. 43 and 8 mg boron/kg/day, respectively). The effects appear to be reversible upon cessation of exposure. Neurotoxicity testing is not recommended because animal studies do not appear to be predictive of this effect.

Boundaries. The boundaries of this category are not yet well defined for health effects. All of the toxicity data are on boric acid or borax. A molecular weight cutoff of 1,000 is proposed, but there is no information from available toxicity data on a proper water solubility cutoff.

General Testing Strategy. The OECD reproductive toxicity screen (OECD 421) with special additional attention to hematology. If this screen is positive for reproductive toxicity, a reproductive fertility study in rats according to the OPPTS Harmonized Test Guidelines (870.3800) is recommended.

In cases in which exposures are exclusively dermal, a dermal absorption study (either in vivo or in vitro) could be conducted to refine the dermal risk assessment. If the in vivo study is selected, the test material should not be corrosive. If there is some uncertainty as to the corrosivity of the neat test material, a dermal irritation study should be undertaken first. If the neat material is corrosive, dilution to a noncorrosive concentration with a vehicle such as acetone or the alcohol used to make the ester is recommended.

Environmental Toxicity:

Most of the toxicity information for boron compounds is for boric acid and sodium tetraborate. These boron compounds show low acute toxicity towards fish (250.0 mg/L as a mean acute toxicity value) and daphnids (70.0 mg/L as a mean acute toxicity value), but moderate toxicity towards green algae (20.0 mg/L as a mean EC50 value). However, these compounds exhibit large acute to chronic ratios (ACR) towards fish (125 as a mean ACR) and the difference between the EC50 value and the chronic value (ChV) in green algae is large (about 117 as a mean difference). The mean ACR for daphnids is 8. The mean ChVs for fish, daphnids, and green algae are 2.0 mg/L, 9.0 mg/L, and 0.170 mg/L, respectively. Green algae appears to be the most sensitive group of species with respect to boric acid and sodium tetraborate.

There are only screening data for fish for borate esters, specifically, only for tributylborate. These screening data showed no effects at 10.0 mg/L for 24 hours towards three species of fish. However, the purity of the tributylborate was not given.

The only data for boranes are for tert-butylamine borane. These data are: fish 96-h LC50 = 13.0 mg/L, daphnid 96-h LC50 = 0.700 mg/L, green algal 7-d EC50 = 3.0 mg/L, and algal ChV = 0.300 mg/L.

The only toxicity information for boron hydrides are for mammals. These data show that all boron hydrides are highly toxic and more toxic than borates.

The major environmental hazard concerns for this category are for chronic toxicity towards fish and toxicity towards green algae.

Since there is no SARs for boron compounds, hazard profiles are developed using the nearest analog(s).

Boundaries. Boron compounds must have water solubilities equal to or greater than 1.0 µg/L (ppb) and molecular weights generally need to be near or below 1000.

Environmental Fate. Certain borates are subject to hydrolysis under environmentally realistic conditions.

General Testing Strategy.

The following testing strategy will address aquatic toxicity concerns:

I. Release to Aquatic Ecosystems:

Tier 1a. If the hydrolysis rate for any member of this class is predicted to be slow ($t_{1/2} > 2$ days) or if hydrolysis will result in one or more products which are expected to be just as toxic as the parent borate, then the fish and daphnid acute toxicity tests from the aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR 797.1400 or OPPTS 850.1075) and daphnids (40 CFR 797.1300 or OPPTS 850.1010) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should equal the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

The algal toxicity testing (40 CFR 797.1050 or OPPTS 850.5400), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis equal to the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

If there is no significant risk from the PMN after the results of the environmental base set of tests have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 1b. If the hydrolysis rate for any member of this class is predicted to be rapid ($t½ <$ 2 days) and if hydrolysis will result in products which are expected to be significantly less toxic as the parent borate, then hydrolysis as a function of pH and temperature (40 CFR 796.3510 or OPPTS 835.2130) will be recommended.

If the resulting hydrolysis t½ is < 2 days, then this result will be integrated into a new risk assessment for the PMN. However, the resulting hydrolysis t½ > 2 days, then the environmental base set will be recommended.

If there is no significant risk from the PMN after the results of the environmental base set of tests have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR 797.1600 or OPPTS 850.1400), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; and statistical analysis of effective concentrations at days 7, 14, 21, and 28.

Daphnid chronic toxicity testing (40 CFR 797.1330 or OPPTS 850.1300), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21.

Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation	40 CFR 796.3100 or OPPT 835.3100
Modified Sturm Test	40 CFR 796.3260 or OPPT 835.3110
Closed Bottle Test	40 CFR 796.3200 or OPPT 835.3110
Modified OECD Screening Test	40 CFR 796.3240 or OPPT 835.3110
Modified MITI Test (I)	40 CFR 796.3220 or OPPT 835.3110
Modified AFNOR Test	40 CFR 796.3180 or OPPT 835.3110

II. Release to terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

July, 1991; revised August, 1997.

Category: Cationic Dyes Environmental Toxicity

Definition. Any dye bearing one or more net permanent positive charges is considered to be a member of this class. A "typical" new chemical of concern is a water soluble monoazo dye with a single delocalized positive charge.

Hazard Concerns. Water soluble cationic dyes are toxic to fish, daphnids, and algae. Poorly soluble dyes tend to be toxic only to algae. No relationship between structure and activity has been found for cationic dyes.

Boundaries. There are no established boundaries for cationic dyes. There is no molecular weight threshold - one dye with a molecular weight of 3,000 and bearing four positive charges was found to be toxic to fish.

Testing. To adress environmental concerns, the base set of environmental toxicity tests (i.e., the fish acute toxicity test, the daphnid acute toxicity test and the green algal toxicity test) is recommended. These tests are to be done using the static method and nominal concentrations. In addition, two additional fish acute toxicity tests are recommended with known amounts of humic acid added to the dilution water. This testing is necessary to measure the mitigating effects of dissolved organic carbon (DOC) on the toxicity of the cationic dye. One test will be done with 20 mg humic acid/L in dilution and the second test will have 10 mg humic acid/L in dilution water. Total organic carbon (TOC) will be measured three times in each test and the TOC of the clean dilution water will also be measured at the beginning of the test.

If DOC mitigates the environmental risk to water column organisms, then testing using natural sediments and organisms known to ingest sediment may be recommended.

March, 1990

Category: <u>Cationic (quaternary ammonium) surfactants</u> Environmental Toxicity

Definition.

Any cationic surfactant is a member of this category, for example:

$$
\begin{array}{l}
\quad CH_3 \\
\quad | \\
CH_3\text{-}N^+\text{-}(CH_2\text{-})_{15}\text{-}CH_3 \;\; Br^- \\
\quad | \\
\quad CH_3
\end{array}
$$

Hazard Concerns. Cationic surfactants are biocidal to a wide array of species in the environment. Toxicity increases exponentially with increasing carbon chain length up to 16 carbons and then decreases with increasing chain length. QSAR (quantitative structure-activity relationships) have been developed to predict toxicity.

Boundaries. Little toxicity is observed when the carbon chain length exceeds 22. Tight ion pairs will not be significantly toxic.

<u>General Testing Strategy</u>. To address ecotoxicity concerns, base set aquatic toxicity testing in algae, daphnids, and fish, plus humic acid testing in fish (20 mg/L humic acid in dilution water and 10 mg/L) is recommended. All testing uses static method, nominal concentrations.

March, 1990

Category: Cobalt Environmental Toxicity

This category includes but is not limited to inorganic and organic compounds of cobalt (Co), e.g., soluble cobalt cations, cobalt esters, and organocobalt compounds.

Hazard Concerns.

Most of the toxicity information for inorganic cobalt compounds is for the soluble salts: chloride, nitrate, and sulfate. There are no known data for organoCo compounds, organic acid chelates with Co, or for Co esters.

The best toxicity data for Co are listed below with predicted (P) and measured (M) toxicity values indicated and effective concentrations in mg Co/L (ppm):

fish (FHM) 96-h LC_{50}	=	48.0 M S,?,H130,Cl E86
daphnid 48-h LC_{50}	=	1.32 M Cl B&S74
daphnid 48-h LC_{50}	=	1.11 M S,N,H45,Cl B&C72
WQ 2° acute value	=	0.195 P S96
green algal 7-d EC_{50}	=	0.160 M S,? NO3,Cl,SO4 St81
RTELS 28-d LC_{50}	=	0.470 M SR12h,?,H104,NO3 B78
fish $ChEC_{20}$	=	0.810 M S96
fish Chronic Value (ChV)	=	0.290 M S96
fish ACR	=	170.0 P
daphnid $ChEC_{20}$	=	0.004 M S96
daphnid ChV	=	0.010 M S,N,H45,Cl B&C72
daphnid ChV	=	0.005 M S96
daphnid ACR	=	110.0 P B&C72
WQ 2° chronic value	=	0.003 P S96
algal ChV	=	0.040 P EC50÷ChV=4

Abbreviations:

ACR = acute-to-chronic ratio;
Ch = chronic;
ChV = chronic value;
CC = concern concentration;
ELS = early life stage;
FHM = fathead minnow;
H = hardness as $CaCO_3$;
N = nominal concentrations;
? = method unknown;
RT = rainbow trout;
S = static method;
SR12h = static renewal method with renewals every 12 hours; and

WQ = water quality value.

Predictions were based on SARs for inorganic Co compounds; pH 7; hardness <180.0 mg/L as $CaCO_3$; 100% active ingredients; mean measured concentrations of Co; and total organic carbon (TOC) <2.0 mg/L;

Environmental concerns for Co compounds:

moderate concern for acute toxicity to fish;
moderate concern for acute toxicity to daphnids;
high concern for toxicity to green algae;
moderate concern for chronic toxicity to fish;
high concern for chronic toxicity to daphnids;
high concern for toxicity to green algae;

assessment factor (AsF)	=	10.0
COC for fish	=	0.030
COC for daphnids	=	0.001
COC for green algae	=	0.004

The aquatic toxicity for the chelates and esters of Co are expected to be less than predicted using toxicity data based on the soluble ion and with a MW adjustment.

The aquatic toxicity for organoCo could be higher than predicted using toxicity data based on the soluble ion and with a MW adjustment because the organic portion could enhance uptake in aquatic organisms. It is assumed that (1) the MWs of organoCo compounds would have to be less than 1000 daltons and (2) the log K_{ow} of any organoCo would have to be less than 8.0 for toxicity to aquatic organisms to occur. It is also assumed that the aquatic toxicity of organoCo compounds will increase with increasing K_{ow} when the log K_{ow} <8.0.

The major environmental toxicity concerns for this category are for chronic toxicity towards daphnids and toxicity towards green algae. The acute-to-chronic ratios of Co towards fish and daphnids are both greater than 100. The SAR method for Co compounds is the nearest analog(s) method.

Boundaries.

Cobalt compounds must have water solubilities equal to or greater than 1.0 µg/L (ppb) and molecular weights generally need to be near or below 1000. The log K_{ow} of organoCo compounds has to be <8.0.

Fate:

General Testing Strategy: I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (OPPTS 850.1075) and daphnids (OPPTS 850.1010) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; and solvent can be used to assist the test chemical to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the test chemical beyond its aqueous solubility limit. Stock solutions in water should be adjusted to pH near 7.0.

The algal toxicity testing (OPPTS 850.5400), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; and solvent can be used to assist the test chemical to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the test chemical beyond its aqueous solubility limit. Stock solutions in water should be adjusted to pH near 7.0.

If there is no significant risk from the test chemical after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. For organoCo compounds, or chelates or esters of Co, aerobic biodegradability according to either of the following test guidelines:

Ready Biodegradability	OPPTS 835.3110
Sealed Vessel CO2 Production Test	OPPTS 835.3120

If there is no significant risk from the test chemical after the results of biodegradation testing have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 3.

Tier 3. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (OPPTS 850.1400), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; solvent can be used to assist the test chemical to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the test chemical beyond its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because the 7-d ELS toxicity test may underestimate chronic toxicity measured by the 28-d ELS toxicity test when the Chronic Values are compared. Stock solutions in water should be adjusted to pH near 7.0.

Daphnid chronic toxicity testing (OPPTS 850.1300), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; solvent can be used to assist the test chemical to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the test chemical beyond its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because the fish 7-d ELS toxicity test may underestimate chronic toxicity measured by the fish 28-d ELS toxicity test when the chronic values are compared.

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

References.

B78   = Birge. 1978. USDOE Tech Info
B&C72 = Biesinger&Christensen. 1972. J Fish Res Brd Can 29:1691
B&S74 = Baudouin&Scoppa. 1974. Bull Environ Contam Toxicol 12:745
E86   = Ewell etal. 1986. Environ Toxicol Chem 5:831
S96   = Suter, GW. 1996. Environ Toxicol Chem 15:1234
St81 = Stokes. 1981. J Plant Nutrit 3:667

September, 1996.

Category: Diazoniums Environmental Toxicity

This category includes only aromatic diazoniums ($N{\equiv}N^+$). Aliphatic diazoniums are very explosive and are only used as synthesizing agents. Aromatic diazoniums are used as fungicides on seeds and in soil, e.g., Fenaminosulf. It is known that diazoniums need to be absorbed to be toxic. Test data submitted to the Agency in the New Chemicals Program showed that diazo compounds with a number average molecular weight (MWn) > 1000 have no effects at saturation to fish in the acute toxicity test. Therefore, compounds with MWn's > 1000 will be excluded from this category regardless of water solubility. In the NEAT state, diazoniums are solids, i.e., salts, and are most are soluble in aqueous media. Acute toxicity for diazoniums is assumed to be limited by the octanol/water partition coefficient (K_{ow}; with a missing fragment for $N{\equiv}N^+$) and MW. Above a log K_{ow} value of => 8.0 and/or MW = 1000, diazoniums are not expected to be toxic at saturation during 96-h exposures. Diazoniums are expected to be similar to anilines with respect to their K_{ow} cutoff value for acute toxicity. This assumes that the missing fragment for $N{\equiv}N^+ = -1.0$. The acute toxicity of anilines diminishes at about a log $K_{ow} = 7.0$ (Veith and Broderius 1987). There are no known K_{ow} limits for chronic toxicity at this time, but it may not be much above a log $K_{ow} = 10.0$ for diazoniums. Future testing will determine this K_{ow} limit.

Hazard Concerns. The acute toxicity for diazoniums has been determined through SAR Analysis:

$$\log \text{fish 96-h } LC_{50} \text{ (millimoles/L)} = -2.456 - 0.331 \log K_{ow}$$

based on a log K_{ow} for the diazonium using CLOGP Ver. 3.3 with a missing fragment for $N{\equiv}N^+$, N = 3, and $R^2 = 0.98$. Acute toxicity values are assumed to be valid through log $K_{ow} = 8.0$.

Daphnids are assumed to have similar sensitivity to fish, but green algae are expected to be more sensitive based on the use of diazoniums as fungicides.

Fate: Diazonium fungicides, e.g., Fenaminosulf, are sensitive to light but is stabilized with Na sulphite. Fenaminosulf is stable in alkaline media. Diazoniums are also used in photography, e.g., diazo reproduction paper and film. Therefore, diazoniums are expected to be subject to rapid direct and indirect photolysis under environmentally realistic conditions. Diazoniums are also expected to slowly hydrolyze to phenols.

Boundaries.: There are no known lower boundaries. The upper boundaries will be based on K_{ow} and MW. Acute toxicity expected with log $K_{ow} < 8.0$ with a missing fragment for $N{\equiv}N^+$.; no effects at saturation during 96-h exposures when log K_{ow} >= 8.0. Chronic toxicity has no known upper bound for log K_{ow}, but it is probably near 10.0 with a missing fragment for $N{\equiv}N^+$. MW must be < 1000. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log K_{ow} is >= 10.0, chronic toxicity testing with fish and daphnids will be recommended.

<u>General Testing Strategy</u>.

I. <u>Release to Aquatic Ecosystems</u>:

Tier 1. The <u>aquatic</u> base set of environmental toxicity tests will be recommended for aquatic exposures. Since diazoniums compounds are photosensitive to <u>uv</u> light, it is best to avoid the use of fluorescent lights in toxicity tests. If they are used, then glass filters should be used. The acute toxicity tests for fish (CFR §797.1400) and daphnids (CFR §797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

The algal toxicity testing (CFR §797.1050), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis cannot exceed the PMN's aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

If there is no significant risk from the PMN after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Direct and Indirect Photolysis Screening Test (40 CFR 796.3765). If $t½ \leq 2$ days, go to Tier 3; if $t½ > 2$ days, go to Tier 4.

Tier 3a. If $t½ \leq 2$ days and photolysis products are known and/or identified, then assess photolysis products for environmental hazards.

Tier 3b. If $t½ \leq 2$ days and photolysis products are not known and/or identifiable, then prepare a stock solution of PMN using the standard humic-containing solution described in the direct and indirect photolysis screening test [40.796.3765 (b)(2) and (c)(2)], expose to sunlight for at least 6 half-lives (t½), and test photolysis products for toxicity with most sensitive species from environmental base set. For example, the most sensitive species from the environmental base set has an EC50 value = 2.0 mg PMN/L (based on 100% active ingredients [AI]), therefore, prepare a 5.0 mg PMN per liter stock solution based on 100% AI using the standard humic-containing solution. This stock solution is exposed to sunlight for at least 6 half-lives to ensure that all of the PMN has been photolyzed, and then this stock solution is used to retest the most sensitive aquatic species to determine if the photolysis products of the PMN are more or less toxic that the PMN.

Tier 4. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (CFR §797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the PMN; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because Van Leeuwen et al (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen);

Daphnid chronic toxicity testing (CFR §797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because Van Leeuwen et al (1990) have demonstrated that the fish 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the fish 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen).

Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation	40 CFR 796.3100
Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test, the avian acute oral toxicity test, and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, avian reproduction toxicity test, and the soil microbial community bioassay.

References.

Van Leeuwen CJ, Adema DMM, and Hermens J. 1990. Quantitative structure-activity relationships for fish early life stage toxicity. Aquatic Toxicology 16:321-334.

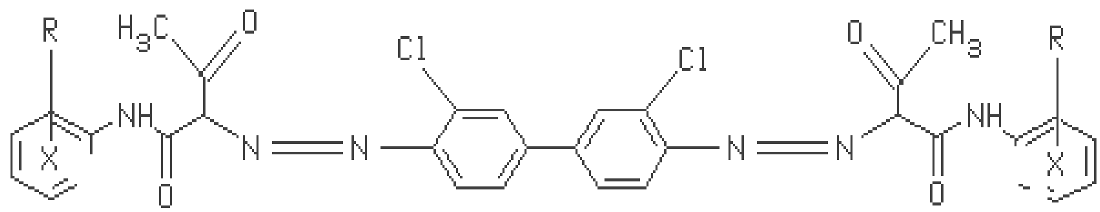
Veith GD and Broderius SJ. 1987. Structure-toxicity relationships for industrial chemicals causing type (II) narcosis syndrome. In Kaiser KLE (ed), QSAR In Environmental Toxicology - II, p 385-391. Reidel Publishing Company.

November, 1991

Category: <u>Dichlorobenzidine-based Pigments</u> Human Health
Environmental Toxicity

Other Names: Diarylide Pigments, DCB Pigments, Pigment Yellows

Definition: Any diazo pigment containing the substructure, dichlorobenzidine, and coupled with acetoacetanilide.



R = substituent of the coupling component

Hazard Concerns. There are oncogenicity/mutagenicity concerns for dichlorobenzidine-based pigments based on the potential release of 3,3'-dichlorobenzidine and on the presence of residual (unbound) dichlorobenzidine. DCB is a known animal carcinogen and a suspect human carcinogen. In addition, DCB is known to bioconcentrate in the tissues of aquatic organisms.

Boundaries. Concern for the intact pigment is restricted to uses at temperatures exceeding 200ºC. Data submitted to the Agency under TSCA section 8(e) show that DCB pigments break down to release DCB as a vapor from colored polymers when heated to extrusion temperatures (> 200ºC) and, from sheetmetal coatings during curing. Though little information exists on the biodegradation of pigments in sediments, data on other low water soluble colorants, indicate that biodegradation may occur over a period of months, possibly resulting in the release of DCB.

<u>General Testing Strategy.</u>

EPA's New Chemicals Program considers the following tests to be appropriate to address the potential for DCB pigments to pose a significant risk to health or the environment:

1. Monitoring data to detect the presence of DCB under actual conditions of use; temperature, dwell time, % pigment in polymer or coating, and type of polymer or coating.

2. If there are releases to water, an anaerobic biodegradation assay.

References:

Appleton HT, Sikka HC. 1980. Accumulation, elimination, and metabolism of 3,3'-dichlorobenzidine in the bluegill sunfish. Environ Sci Technol 14:50-54.

Pliss GB. 1963. On some regular relationship between carcinogenicity of aminobiphenyl derivatives and the structure of the substance. Acta Unio Int Cancrum 19:499-501.

Stula EF, Sherman H, Reinhardt CF. 1975. Experimental neoplasia in rats from oral administration of 3,3'-dichlorobenzidine, 4,4'-methylene-bis(2-chloroaniline), and 4,4'-methylene-bis(2-methylaniline). Toxicol Appl Pharmacol 32:159-176.

Stula EF, Barnes JR, Sherman H. 1978. Liver and urinary bladder tumors in dogs from 3,3-dichlorobenzidine. 1978. J Environ Pathol Toxicol 1:475-490.

TSCA Section 8(e) Documents:

8EHQ-0490-0962 INIT

8EHQ-0590-0962 SUPPL

8EHQ-0690-0962 FLWP

8EHQ-0790-0962 SUPPL

8EHQ-0890-0962 SUPPL

March, 1994

Category: <u>Dithiocarbamates</u> Environmental Toxicity

This category includes N,N-dialkyldithiocarbamates (DDC); ethylenebisdithiocarbamates (BDC); and their metal salts which include but are not limited to zinc, sodium, iron, manganese, copper, lead, mercury, silver and selenium. The alkyl groups of the DDCs generally include, methyl through butyl, but may be larger. This category also includes the degradation products of DDC and BDC which may include disulfide moieties, sulfide moieties, thiourea moieties, urea moieties, polymeric sulfide moieties, dithizaole-3-thiones, cyclic thioureas and cyclic ureas as indicated in the generic environmental hazard assessment.

$$H_3C — (CH_2)m — (O\text{-}CH_2\text{-}CH_2\text{-})n — OH$$

alkyl ethoxylate

$$H_3C — (CH_2)m — (O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-})n — OH$$

alkyl propoxylate

Hazard Concerns: Many members of this category are commercial insecticides, fungicides, disinfectants, rodenticides, antioxidants, slimicides, algalicides, bactericides and heavy metal chelators. Their mode of toxic action apparently results from interference with metallo-enzymes in living cells; the toxicity has been attributed to either DDCs and BDCs or their degradation products. All of the known dithiocarbamates are acutely toxic to fish, algae and bacteria at < 10 mg/L, and to aquatic invertebrates at < 1 mg/L. Chronic toxicity to fish and aquatic invertebrates ranges from 0.001 to 2 mg/L and 0.011 to 0.111 mg/L, respectively. In general, the SARs for the dithiocarbamates and their degradation products are sigmoidal with acute and chronic toxicity increasing with increasing Kow. The sigmoidal relationship between Kow and toxicity of the dithiocarbamates is very poor statistically. Consequently, toxicity predictions will be made using either the closest analog or averaging data for the two closest analogs which bracket the dithiocarbamate under question. The SAR for the degradation products is much more robust and a series of SARs will be used to predict acute toxicity of degradation products toward fish, daphnids and Photobacterim phosphoreum; and chronic toxicity toward fish, daphnids and green algae.

Boundaries: There are no known lower boundaries. The upper boundaries are based on K_{ow} and MW. When the log Kow value is < 5 mg/L, the environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log K_{ow} is between 5 and < 19, only chronic toxicity testing will be recommended. When the log K_{ow} is ≥ 19 (CLOGP), no testing will be requested because no toxic effects at saturation will be expected. Generally, members of this category will have MWs of less than 1000.

General Testing Strategy

Tier 1. The acute aquatic base set of environmental toxicity tests will be recommended for aquatic exposures and the terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm acute toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures.

Tier 2. If acute toxicity testing indicates a significant risk, then chronic toxicity with fish and aquatic invertebrates will be recommended as well as aerobic biodegradation testing.

Aerobic biodegradability can be determined using one of the following test guidelines, listed in approximate order of preference:

Aerobic aquatic biodegradation	40 CFR 796.3100
Modified Sturm test	40 CFR 796.3260
Closed bottle test	40 CFR 796.3200
Modified OECD screening test	40 CFR 796.3240
Modified MITI test (I)	40 CFR 796.3220
Modified AFNOR test	40 CFR 796.3180

August 1989; revised November 1995

Category: <u>Epoxides</u>

Human Health
Environmental Toxicity

Definition. Any molecular structure containing one or more epoxy groups is considered to be a member of the category:

```
   O
  / \
-C---C-
 |   |
```

Hazard Concerns. Health concerns for epoxides are for cancer and reproductive effects based on data for several analogous chemicals. There is greater concern for primary epoxides,

```
   O
  / \
-C---CH
 H   H
```

than for epoxides with substitutions on both of the epoxy carbons. Environmental toxicity is a function of the octanol-water partition coefficient. Compounds with log P's >5 act as neutral organics producing simple narcosis, but at lower log P's, epoxides display toxicity greater than that predicted for simple narcotics. A QSAR (quantitative structure-activity relationship) to predict the environmental toxicity of epoxides is under development.

Boundaries. Structures with epoxy equivalent weights of ≥1,000 are presumed not to pose a hazard under any conditions. Concerns are confined to those species with molecular weights <1,000. Health concerns are restricted to species with molecular weights <500 if exposure is limited to the dermal route.

Testing. To address health concerns the following tests are usually recommended for members of this class: (1) a lifetime cancer bioassay by the expected route of exposure, and (2) a 90-day subchronic with attention to pathology of the reproductive organs. To address ecotoxicity concerns, base set acute aquatic toxicity testing (algae: static method, daphnid and fish: flow-through method, all measured concentrations).

September, 1988

Category: Esters Environmental Toxicity

This category includes all esters, polyesters, vinyl esters, allylic esters, propargylic esters, aliphatic esters, aromatic esters, carboxylic acid esters, and sulfonate esters. These compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will be excluded from this category. Acute toxicity for esters which are liquids at room temperature is known to be limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of => 5.0, esters show no effects at saturation during 96-h exposures (Veith et al 1984). Esters which are solids at room temperature may show no toxicity at saturation at lower K_{ow} values depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no acute toxicity will be observed at saturation. For solids, the no-effects-at-saturation point has to be determined on a case-by-case basis. The K_{ow} limit for chronic toxicity is set at a log K_{ow} = 8 for liquid esters. For solid esters, chronic toxicity testing will determine this K_{ow} limit.

Hazard Concerns. The toxicity for simple esters has been determined through SAR Analysis (Clements 1988). Esters are known to be more toxic than neutral organic chemicals, and this excess toxicity decreases with increasing K_{ow}. The toxicity for vinyl esters, allylic esters, and propargylic esters is expected to be greater than for simple esters. Again, the additional excess toxicity of these vinyl esters, allylic esters, and propargylic esters is expected to decrease with increasing K_{ow}.

Members of this category exhibit toxicity ranging from low toxicity (i.e., > 100 mg/L) to high toxicity (i.e., < 1 mg/L) depending on their K_{ow}, MW, and melting point.

Boundaries. There are no known lower boundaries. The upper boundaries will be based on K_{ow} and MW. Acute toxicity is expected when log K_{ow} < 5.0; no effects at saturation during 96-h exposures when log K_{ow} > 5.0. The upper boundary for chronic toxicity is 8.0. MW will be < 1000. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log K_{ow} is > 5.0, chronic toxicity testing with fish and daphnids will be recommended.

Fate: Esters are subject to both abiotic and biotic hydrolysis, i.e., ester hydrolysis, and aerobic biodegradation. Aerobic biodegradation is expected to be the dominant route of transformation in the environment.

General Testing Strategy.

I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR §797.1400) and daphnids (40 CFR §797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit; and solvent can be used to assist the ester to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the ester beyond its aqueous solubility limit.

The algal toxicity test (40 CFR §797.1050) should be done with the static method; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the ester; and solvent can be used to assist the ester to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the ester beyond its aqueous solubility limit.

If there is no significant risk from the ester after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation	40 CFR 796.3100
Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

If there is no significant risk from the ester after the results of the aerobic biodegradation testing have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 3.

Tier 3. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR §797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested chemical; solvent can be used to assist the ester to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the ester beyond its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because Van Leeuwen et al (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen). Both anilines and esters are more toxic than predicted based on narcosis alone, i.e., both esters and anilines have excess toxicity due to a more specific mode(s) of toxic action. A seven day exposure may not allow enough time for this excess toxicity to be expressed either because of not enough exposure and/or not enough time for metabolic activation.

Daphnid chronic toxicity testing (40 CFR §797.1330), with flow-through methods;

measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the ester; solvent can be used to assist the ester to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the ester above its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test (Van Leeuwen et al 1990).

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test, the avian acute oral toxicity test, and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, the avian reproductive toxicity test, and the soil microbial community bioassay.

References.

Clements, RG (editor). 1988. Estimating toxicity of industrial chemicals to aquatic organisms using structure-activity relationships. EPA-560-6-88-001. Washington, DC: Environmental Effects Branch, Health and Environmental Review Division, Office of Toxic Substances (TS-796), United States Environmental Protection Agency. Available from the National Technical Information Service, Springfield, VA 22161, PB89-117592.

Van Leeuwen CJ, Adema DMM, and Hermens J. 1990. Quantitative structure-activity relationships for fish early life stage toxicity. Aquatic Toxicology 16:321-334.

Veith GD, DeFoe D, and Knuth M. 1984. Structure-activity relationships for screening organic chemicals for potential ecotoxicity effects. Drug Metabolism Reviews 15(7):1295-1003.

November, 1991

Category: Ethylene Glycol Ethers Human Health

Definition. The ethylene glycol ether category is defined as follows:

$R\text{-}(OCH_2CH_2)_n\text{-}OR'$

$n = 1, 2, \text{ or } 3$

R = alkyl C_7 or less or phenyl or alkyl substituted phenyl

R' = H or alkyl C_7 or less or any group that can be chemically or metabolically removed to yield a glycol ether

Hazard Concerns. Short-chain ethylene glycol ethers are absorbed by all routes of exposure and have caused irritation of skin, eyes, and mucous membranes; hemolysis, bone-marrow damage, and leukopenia of both lymphocytes and granulocytes; direct and indirect kidney damage; liver damage, immunotoxicity, and central nervous system (CNS) depression. Short-chain ethylene glycol ethers are also developmental and reproductive toxicants. 2-Phenoxyethanol is known to cause hemolysis and eye irritation.

Boundaries. There is evidence that developmental toxicity is reduced going from the methyl to the butyl ether, and that it is reduced going from the ethylene glycol to the triethylene glycol. However, there is still a concern for maternal toxicity as reflected in developmental and subchronic toxicity studies. The systemic toxicity of longer-chain glycol ethers and alkylphenyl glycol ethers is uncertain because data are not available. The alkyl chain length of C_7 or less was chosen as a boundary for short-chain ethylene glycol ethers based on the available data.

General Testing Strategy

The New Chemicals Program considers the following tests to be the most appropriate for ethylene glycol ethers with sufficient exposure to potentially pose an unreasonable risk:

Tier 1 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screen Test (OECD Guideline 422). If signs of hematuria are seen red and white blood cell counts should be taken 2 days later except for female animals during pregnancy and lactation.

Tier 2 - The need for further testing would be determined by the results of Tier 1. This could include any of the following tests.

Prenatal Developmental Toxicity via the most appropriate route (40 CFR 799.9370)
2-Generation Reproduction Study via the most appropriate route (40 CFR 799.9380)
90-Day Subchronic Study via the most appropriate route (40 CFR 799.9346 - inhalation route; 870.3250 - dermal route; 870.3150 - oral route)

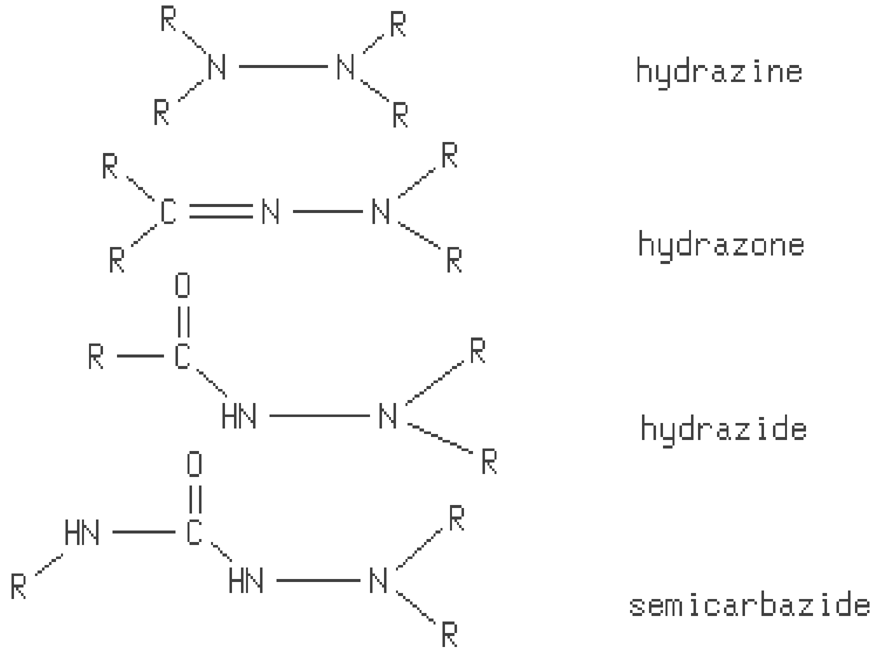
Immunotoxicity Study via the most appropriate route (OPPTS 870.7800)

June 1992, revised December 1997

Category: <u>Hydrazines and Related Compounds</u>

Human Health
Environmental Toxicity

Definition: Any structure containing one or more of the following groups is considered to be a member of the category:



R is unlimited except by molecular weight

Hazard Concerns: Concerns for carcinogenicity and chronic effects to liver, kidney, and blood are based on data for a number of hydrazines and related chemicals. In humans, hydrazine, itself, may affect the central nervous system, liver, and kidneys. The toxic effects of hydrazine exposure to humans may range from mild skin and eye irritation, and skin sensitization, to severe irritation and burns, pulmonary edema, CNS depression, as well as liver and kidney damage, which can lead to death. Hydrazine may also present a serious hazard to plant life and aquatic organisms. Ecotoxicity concerns are based on structure activity relationships (SAR) using data for a number of hydrazines and hydrazides. Hydrazine itself (N_2H_4), is known to be acutely toxic to aquatic organisms at low levels, algae at < 100 ppb, 200 ppb for fish, and 30 ppb for daphnids.

Boundaries: There are no established boundaries for this category. The "typical" new chemical member of the category is a discrete (class I) chemical with a molecular weight <500. There is a greater concern for chemicals with few substitutions on the functional group than for those with multiple substitutions.

General Testing Strategy

EPA considers the following tests to be appropriate to address health and ecotoxicity concerns:

1. Lifetime cancer bioassay by the expected route of exposure in two species of rodents (40 CFR 798.3300).

2. 90-Day subchronic in one species of rodent by the expected route of exposure to assess effects to the liver, kidney, and blood (40 CFR 798.2650).

3. Base-set ecotoxicity testing to include fish (40 CFR 797.1400) using the flow-through method, daphnids (40 CFR 797.1300) using the flow-through method and algae (40 CFR 797.1050) using the static method, all measured concentrations.

Results of the acute ecotoxicity testing may trigger chronic fish (40 CFR 797.1600) and daphnid (40 CFR 797.1350) testing.

4. Environmental fate testing including, as appropriate, melting point (40 CFR 796.1300) or boiling point (40 CFR 796.1220), water solubility (40 CFR 796.1840 or 796.1860), log K_{ow} (40 CFR 796.1550, 796.1570 or 796.1720), vapor pressure (40 CFR 796.1950) and hydrolysis (40 CFR 796.3500). For aromatic hydrazines and related compounds, the following additional testing is recommended; direct and indirect photolysis (40 CFR 796.3765), and aerobic biodegradation.

Aerobic biodegradability can be determined using one of the following test guidelines, listed in approximate order of preference:

Aerobic aquatic biodegradation	40 CFR 796.3100
Modified Sturm test	40 CFR 796.3260
Closed bottle test	40 CFR 796.3200
Modified OECD screening test	40 CFR 796.3240
Modified MITI test (I)	40 CFR 796.3220
Modified AFNOR test	40 CFR 796.3180

References.

1. Bhide, S.V., R.A. D'Souza, M.M. Sawai, & K.J. Ranadive (1976). International Journal of Cancer 18: 530.

2. Biancifiori, C (1970). Journal of the National Cancer Institute 44: 943.

3. Biancifiori, C (1971). Lav. 1st Anat. Istol. Pat., Univ. Studi Perugia 31: 5.

4. Biancifiori, C., E. Bucciarelli, D.B. Clayson, & F.E. Santilli (1964). British Journal of Cancer 18: 543.

5. Hydrazine-RM2 Exit Document. OPPT Office Director's Meeting, Monday, December 13, 1993.

6. Juhasz, J., J. Balo, & B. Szende (1966). Nature (London) 210: 1377.

7. Juhasz, J., J. Balo, & B. Szende (1967). Z. Krebsforsch 70: 150.

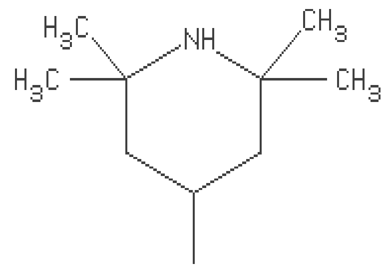
8. Toth, B. (1969). Journal of the National Cancer Institute 42: 469.

9. Toth, B. (1972). International Journal of Cancer 9: 109.

September, 1988; revised June, 1994, revised October 1995.

Category: <u>Hindered Amines</u> Human Health

Definition. The category is at present not well defined. A "typical" new chemical hindered amine of concern has <u>two</u> or more hindered amine functional groups, usually the 2,2,6,6-tetramethyl-4-piperidinyl group, and is used as a UV light stabilizer.



Hazard Concerns. Health concerns for the category are based on data submitted to the Agency under §8(e) of TSCA for Tinuvin 144 and Chimassorb 944. The data indicate that these hindered amines, and presumably hindered amines similar in structure, are toxic to the immune system, liver, blood, the male reproductive system, and the G.I. tract.

Boundaries. The boundaries of the category are not well defined. Tinuvin 144 has a molecular weight of 685, whereas Chimassorb 944 is a polymer with a number average molecular weight well in excess of 1,000. As a consequence, there is at present no molecular weight cutoff for hindered amines of concern to the new chemical program.

It is assumed that there is little or no dermal absorption of problematic hindered amines because of their high molecular weights. Consequently, hindered amines in the new chemical program are only of concern if there is significant inhalation exposure associated with their manufacture, processing, or use.

<u>General Testing Strategy</u>

For hindered amines found to pose a potentially unreasonable risk, a 90-day oral subchronic test in rats is the recommended test. We have requested that emphasis be placed on hematology, the immune system, and on the male reproductive system.

June 1990; revised March 1995

Category: Imides Environmental Toxicity

This category includes all imides and maleimides. Substitutions may be aliphatic, aromatic, and/or halogens. The mode of toxic action of imides is unknown, but halogenated imides are used as microbial pesticides, specifically, fungicides, bactericides, slimicides, and algicides. It is assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will be excluded from this category. Acute toxicity for imides which are liquids at room temperature is assumed to be limited by the octanol/water partition coefficient (K_{ow}), and the limiting K_{ow} value for acute toxicity is assumed to be about 5.0. The limiting value for chronic toxicity is assumed to be about 8.0. Imides which are solids at room temperature may show no toxicity at saturation at log K_{ow} values < 5.0 depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be observed at saturation. For solids, the no-effects-at-saturation determination has to be made on a case-by-case basis.

Hazard Concerns. The acute toxicity for imides and maleimides towards fish has been determined through SAR Analysis by EPA. The SAR for acute toxicity to fish is defined by the following regression equation:

$$\log \text{96-h LC50} = 1.256 - 0.76 \log K_{ow}$$

where the LC50 is in milliMoles per Liter (mM/L), N = 4, and $R^2 = 0.98$. The acute toxicity of imides towards daphnids is expected to be similar to that of fish, but their toxicity towards green algae is expected to be greater because of their use as microbial pesticides.

Polyimides may be more toxic than predicted using this SAR.

The toxicity of imides towards aquatic organisms can range from low (i.e., > 100.0 mg/L) to high toxicity (i.e., < 1.0 mg/L) depending on their K_{ow} and MW. The higher the K_{ow} and the lower the MW, the higher the toxicity (or the lower the EC50 value).

Boundaries.: There are no known lower log K_{ow} and MW boundaries. The upper boundaries for acute toxicity will be set at a log $K_{ow} \leq 5.0$; chronic toxicity limits will be set at a log $K_{ow} \leq 8.0$. MW will be < 1000 for stable compounds. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures.

General Testing Strategy.

The <u>aquatic</u> base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR 797.1400) and daphnids (40 CFR 797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should equal the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility.

The algal toxicity testing (40 CFR 797.1050), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis equal to the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility.

Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR 797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because Van Leeuwen et al (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen);

Daphnid chronic toxicity testing (40 CFR 797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because Van Leeuwen et al (1990) have demonstrated that the fish 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the fish 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen).

The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test [40 CFR 797.2800], the earthworm acute toxicity test [40 CFR 795.150], and the soil microbial community bioassay [40 CFR 795.3700]) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test [40 CFR 797.2830], the plant uptake test [40 CFR 797.2850], and the soil microbial community bioassay.

References.

Van Leeuwen CJ, Adema DMM, and Hermens J. 1990. Quantitative structure-activity relationships for fish early life stage toxicity. Aquatic Toxicology 16:321-334.

April, 1991

Category: <u>Diisocyanates</u> Human Health

Definition. Any molecular structure containing <u>two</u> or more isocyanate groups is considered to be a member of the category for new chemical purposes:

$$R\text{-}(N{=}C{=}O)_{\geq 2}$$

Members of the class include new isocyanate monomers as well as new oligomers, polymers, prepolymers, or reaction products of existing isocyanate monomers. Most new chemical diisocyanates of concern are polymers or oligomers containing well-known diisocyanate monomers such as toluene diisocyanate (TDI) or 4,4'-methylenediphenyl diisocyanate (MDI).

Hazard Concerns. Diisocyanates are of concern for potential dermal and respiratory sensitization, and for pulmonary toxicity. Based on conflicting animal and human data for respiratory sensitization, the Agency has determined that there is presently not a reliable animal model for testing diisocyanates for potential respiratory sensitization. At this time, it is assumed that all diisocyanates may be potential human respiratory sensitizers.

Most members of the diisocyanate category have not been tested for carcinogenic potential. Though the aromatic diisocyanates [MDI, TDI, dianisidine diisocyanate (DADI)] tested positive and one aliphatic diisocyanate [hexamethylene diisocyanate (HDI)] tested negative in one species, it is premature to make any generalizations about the carcinogenic potential of aromatic versus aliphatic diisocyanates.

Boundaries. Structures with an isocyanate equivalent weight of ≥5,000 are presumed not to pose a hazard under any conditions. Typically, concerns are confined to those species with molecular weights <1,000.

Frequently, new chemical isocyanates are manufactured with a significant excess of isocyanate monomer. Under these circumstances, the excess monomer is usually regarded as more hazardous than the "new" chemical component, and these PMN substances are ordinarily not regulated under §5 of TSCA. For the purposes of risk assessment within the New Chemicals Program, a PMN substance is considered "existing" if more than 50% of the free isocyanate groups in the PMN substance (new chemical component + existing chemical monomer) reside on unreacted monomer(s). This does not relieve a Company, however, of any obligations to submit a PMN for the new chemical isocyanate if indeed it is not listed on the TSCA Inventory.

General Testing Strategy. The following testing is recommended to address the potential for pulmonary toxicity and dermal sensitization.

1. Dermal sensitization (OPPTS 870.2600).

2. 90-day Subchronic inhalation toxicity test in rodents (OPPTS 870.3465).

In addition, appropriate hazard communication needs to be developed and implemented.

Health and Safety Information. The following information provides guidance in developing hazard communication and protective measures language to accompany new diisocyanate chemicals and formulations. It is based on the Agency's current understanding of the hazards associated with diisocyanates and the most effective means to limit exposure.

> **Warnings**. Exposure to diisocyanates may cause the following human health effects: skin irritation and allergic reactions, respiratory irritation, respiratory sensitization, and lung toxicity; some diisocyanates also may cause cancer. The likelihood that these effects will occur depends on a number of factors; among them, the level of exposure, frequency of exposure, part of the body exposed, and sensitivity of the exposed individual.

Symptoms of allergic reaction and respiratory sensitization include rashes, cough, shortness of breath, asthma, chest tightness and other breathing difficulties. There is uncertainty as to the mechanism by which sensitization occurs. In sensitized individuals, exposure to even small amounts of diisocyanates (below government-recommended workplace exposure levels) may cause allergic respiratory reactions like asthma and severe breathing difficulties. <u>It is especially important to note that contact with skin may lead to respiratory sensitization or cause other allergic reactions</u>. In some cases, the effects of diisocyanate exposure may be immediate and life-threatening; in others, the effects may be delayed and occur hours after the exposure has ended. Repeat or prolonged exposure to diisocyanates may also cause irritation to eyes, skin, respiratory tract and lungs, as well as adverse chronic lung effects, like decreased lung capacity and function. Individuals experiencing shortness of breath, tightness in the chest or other problems breathing should seek immediate medical attention.

> **Protective Measures.** In workplaces where individuals handle diisocyanates or coatings or other formulations that contain them, an industrial hygiene and safety program should be operative. Important components of this program include: hazard communication and training on safe handling practices; use of efficient and well-maintained application equipment, engineering controls and personal protective equipment; housekeeping procedures including spill prevention and cleanup practices; and, if feasible, means to measure airborne levels of polyisocyanates and diisocyanates.

During spray applications, workers should take precautions to avoid breathing vapors, mists or aerosols. Inhalation exposures should be limited to <0.05 mg/m^3 as an 8-hour time-weighted average (TWA) for combined polyisocyanates and diisocyanates.[1] Engineering controls should serve as the first, most effective means of reducing airborne polyisocyanate and diisocyanate concentrations; an appropriate NIOSH/MSHA-approved respirator should be used as a secondary tool to lower exposures. Currently, downdraft spray booths and high-volume low-pressure (HVLP) spray guns appear to offer the most efficient technology to reduce inhalation exposures; a maintenance program should always be used to ensure optimal operating efficiencies. To limit dermal contact, individuals should wear impermeable gloves, protective clothing and goggles or glasses with side shields.

May 1990, revised July 1993, February 1995, and February, 1997

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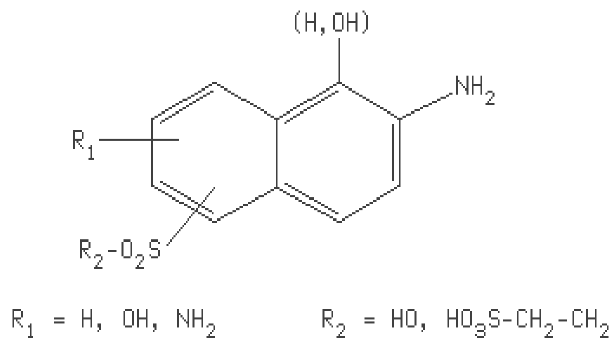
[1]0.05 mg/m^3 or 0.005 ppm TWA is the American Conference of Government Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) for each hexamethylene diisocyanate (HMDI), toluene-2,4-diisocyanate (TDI), and methylene bisphenyl isocyanate (MDI). Also, OSHA has set 0.02 ppm as exposure ceilings for both TDI and MDI.

Category: β-Naphthylamines, Sulfonated Human Health

Definition: Any new chemical whose structure is consistent with the following general structure is considered to be a member of the category of monosulfonated β-naphthylamines:



Included in the category are azo dyes which release a sulfonated β-naphthylamine upon reduction of azo bonds. Also included in the category are N-acetylated sulfonated β-naphthylamines.

Hazard Concerns. Based on analogy to β-naphthylamine *per se*, members of the class are considered potential carcinogens. A number of mono- and disulfonated β-naphthylamines are positive in the Ames assay, and some are active in the mouse lung adenoma assay. The presence of one or two sulfonate groups or the sulfatoethylsulfone group is likely to slow systemic uptake and enhance excretion, however, the extent of these mitigating effects is unknown.

Boundaries. Concern is restricted to sulfonated β-naphthylamines where not more than two sulfonate or sulfatoethylsulfone group(s) are on the ring distal to the β-amino group. The Agency has sufficient data to indicate that β-naphthylamines where a sulfonate group is on the proximal ring are unlikely to be carcinogenic.

General Testing Strategy.

The New Chemicals Program considers the following tests to be the most appropriate for mono- and di-sulfonated β-naphthylamines found to pose an unreasonable risk:

- An Ames test or, for azo dyes, an Ames test with the Prival modification, and

- An unscheduled DNA synthesis test in rat hepatocytes. For azo dyes, it is necessary that the specific sulfonated β-naphthylamine in question be isolated prior to testing.

For both tests, β-naphthylamine is to serve as an additional positive control.

If the results of the genotoxicity testing indicate that the new chemical is genotoxic, a two- year, two-species cancer bioassay would be required.

April 1991, updated June 1999

Category: <u>Lanthanides or Rare Earth Metals</u> Environmental Toxicity

Definition. This category includes inorganic salts, complexes organic acids, and organometallic compounds or lanthanides or rare earth metals. There are 14 naturally-occurring lanthanides or rare earth metals:

Name	Symbol	MW	CASRN
Lanthanum	La	139	[7439-91-0]
Cerium	Ce	140	[7440-45-1]
Praseodymium	Pr	141	[7440-10-0]
Neodymium	Nd	144	[7440-00-8]
Samarium	Sm	150	[7440-19-9]
Europium	Eu	152	[7440-53-1]
Gadolinium	Gd	157	[7440-54-2]
Terbium	Tb	159	[7440-27-9]
Dysprosium	Dy	163	[7429-91-6]
Holmium	Ho	165	[7440-60-0]
Erbium	Er	167	[7440-52-0]
Thulium	Tm	169	[7440-30-4]
Ytterbium	Yb	173	[7440-64-4]
Lutetium	Lu	175	[7439-94-3]

The lanthanide rare earth metals are very similar to each other. Their most important oxidation state is +3 for all. None are known to be essential to biological species. Across the lanthanide series from La to Lu, there is a general or steady decrease in their (1) atomic radii, (2) covalent radii, and (3) radii of their tripositve ions due to the addition of electrons at the 4f electron shell. This decrease in radii leads to a corresponding increase in the polarizing power of their ions and in the stability of complexes of their ions. They all have similar chemistry behaviors.

Hazard Concerns. The only toxicity data available for the lanthanide series are for La [7439-91-0]. Soluble salts of La are known to have high chronic toxicity towards fish, moderate chronic toxicity towards green algae, and low acute toxicity towards daphnids based on exposures in moderately hard water and in terms of mg La/L. Toxicity information are only available for La trichloride [10099-58-8] and La triacetate [917-70-4]. The toxicity profile for La based on available toxicity data, i.e., measured (M) and predicted (P), mg La/L (ppm La), and moderate hardness (i.e., <180.0 mg/L as $CaCO_3$) is:

fish 96-h LC50	<	1.0 P ACR10
daphnid 48-h LC50	=	160.0 M S,N BK59
green algal 96-h EC50	<	1.0 P EC50/ChV=4
fish chronic value(ChV)	=	0.020 M SR12,M H104 B78
daphnid ChV	=	20.0 P ACR10
algal ChV	=	0.150 M S,N BK59

The lanthanides are assumed to be more toxic in soft water than hard water based on data for other heavy metals.

Boundaries. The toxicity of the lanthanide rare earth metals depends on the their physical/chemical properties and the hardness of receiving waters. The toxicity of their salts and their complexes with organic acids are expected to be related to their water solubility, their MWs, and the stability of their complexes. The toxicity of lanthanide organometallic compounds, if they exist, are expected to be related to their octanol/water partition coefficient (Kow).

The most important property determining the toxicity of chemicals derived from lanthanide rare earth metals is their water solubility. Water solubility cannot be estimated accurately and has to be measured. The water solubility of organometallic compounds is expected to decrease as Kow increases. There is no lower bound for Kow and the upper bound cannot be determined at this time since the Kow fragment-constant for any of the lanthanide rare earth metals are not known. In addition to solubility, MW is also an important boundary. Highly stable complexes and organometallics with MWs > 1000 are not expected to be absorbed by aquatic organisms even if they are water soluble. Therefore, only lanthanide rare earth metal-compounds with MWs < 1000 are expected to be toxic.

General Testing Strategy.

I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR §797.1400 or OPPTS 850.1075) and daphnids (40 CFR §797.1300 or OPPTS 850.1010) will be done using the flow-through method; effective concentrations will be based on 100% active ingredients (ai) and mean measured concentrations; the total organic carbon (TOC) concentration of dilution water in the control must be less than 2.0 mg TOC/L; TOC must be measured in the control just prior to the start of the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the compound beyond its aqueous solubility limit; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$. If toxicity mitigation testing is done with humic acid, then the static method with nominal concentrations will be recommended.

The algal toxicity testing (40 CFR §797.1050 or OPPTS 850.5400), should be done with the static method; effective concentrations based on 100% ai and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with no more than 0.300 mg/L EDTA as a final concentration; the TOC of the test/growth medium should be less than 2.0 mg TOC/L; TOC should be measured just prior to the start of the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; and solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the compound beyond its aqueous solubility limit. If toxicity mitigation testing is done with humic acid, then nominal concentrations will be recommended.

If there is no significant risk from the chemical after the results of the environmental base set have been integrated into the risk assessment, then no further testing will be recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR §797.1600 or OPPTS 850.1400), with the flow-through method; effective concentrations based on 100% ai and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; the TOC of dilution water in the control should be less than 2.0 mg TOC/L; TOC should be measured in the controls just prior to and during the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the compound beyond its aqueous solubility limit; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$.

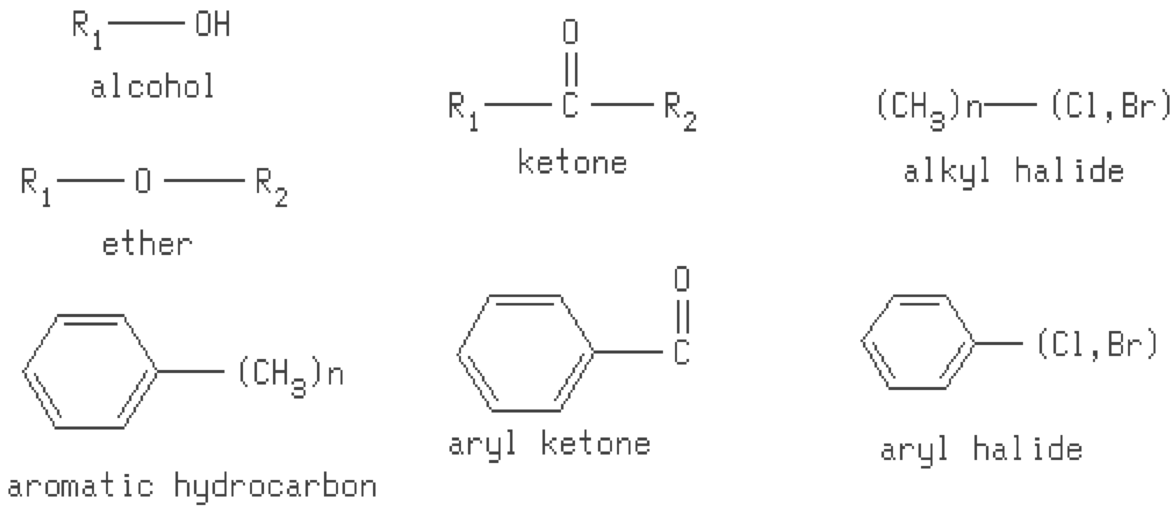
Daphnid chronic toxicity testing (40 CFR §797.1330 or OPPTS 850.1300), with the flow-through method; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; the TOC of dilution water in the control should not exceed 2.0 mg TOC/L; TOC must be measured in the controls just prior to and during the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the compound beyond its aqueous solubility limit; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$.

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests will be recommended for terrestrial exposures. The terrestrial base set includes: the early seeding growth test (OPPTS 850.4230), the earthworm toxicity test (OPPTS 850.6200), the soil microbial community bioassay (OPPTS 850.5100), and the avian acute oral toxicity test (OPPTS 850.2100). Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test (OPPTS 850.4150), the plant uptake test (OPPTS 850.4800), and the avian reproduction test (OPPTS 850.2300 for bobwhite quail or for mallard duck).

February, 1998

Category: Neutral Organics Environmental Toxicity

Definition. This broad category includes non-reactive non-ionizable organic chemicals such as alcohols, ketones, ethers, alkyl halides, aryl halides, and aromatic hydrocarbons.



Hazard Concerns. Neutral organics are environmentally toxic because of their ability to produce simple narcosis in aquatic species. Toxicity is a function of the octanol-water partition coefficient. Compounds with log P's of <5 exhibit toxicity within 96 hours. At log P 5-8, toxicity is apparent only after extended exposure. Compounds with a log P >8 are not toxic at water saturation even after prolonged exposure. There are a number of QSARs (quantitative structure-activity relationships) to predict the toxicity of neutral organics.

Boundaries. The molecular weights of neutral organics of concern are generally less than 1,000. Log P is <8. QSAR predictions of toxicity are constrained by water solubility. If a predicted toxicity level exceeds water saturation, then a longer test is needed to observe toxicity.

General Testing Strategy

To address ecotoxicity concerns, base set acute aquatic toxicity testing (algae (40 CFR 797.1050): static method, daphnid (40 CFR 797.1300) and fish (40 CFR 797.1400): flow-through method, all measured concentrations).

To properly assess any human and environmental toxicity or exposure, certain environmental fate properties, such as aerobic biodegradation, need to be measured. Aerobic biodegradability can be determined using one of the following test guidelines, listed in approximate order of preference:

Aerobic aquatic biodegradation	40 CFR 796.3100
Modified Sturm test	40 CFR 796.3260
Closed bottle test	40 CFR 796.3200
Modified OECD screening test	40 CFR 796.3240
Modified MITI test (I)	40 CFR 796.3220
Modified AFNOR test	40 CFR 796.3180

The physical state and electronic charge of the PMN substance should also be reported.

For some neutral organics (e.g. ketones) direct/indirect photolysis (40 CFR 796.3765 and 796.3700) AND possibly biodegradation testing is recommended.

For some neutral organics (e.g. alkyl halides) hydrolysis testing (40 CFR 796.3510) AND possibly biodegradation testing is recommended.

September 1988; revised October 1995

Category: Nickel Compounds Human Health Environmental Toxicity

Definition. Inorganic and organic compounds of nickel in which there is the potential for uptake of either Ni^{2+} or organonickel.

Hazard Concerns. Nickel compounds e.g., nickel refinery dust, and its major component nickel subsulfide, have been shown to be carcinogenic in humans. Some nickel compounds are known to be genotoxic. IRIS has established an oral RfD for the soluble salts of nickel of 2×10^{-2} mg/kg/d (1992) based on effects on organ weights in a two-year feeding study in rats. In the study, there was a statistically significant reduction in total body weight, higher heart-to-body weight ratios and lower liver-to-body weight ratios than controls. In addition to the effects on organ weights found in the critical two-year study, two other sensitive endpoints exist, neonatal mortality and dermatotoxicity. While no reproductive effects have been associated with nickel exposure to humans, several studies in laboratory animals have demonstrated fetotoxicity.

Soluble inorganic nickel compounds produce acute and chronic toxicity in freshwater and saltwater aquatic organisms over a wide range of concentrations but bioconcentrates only to a small degree. There are no known toxicity data for organonickel compounds.

Boundaries. Any nickel compound that will release Ni^{2+} is considered hazardous. Conversely, there are no available data to suggest that nickel compounds in which the Ni^{2+} is not released may pose a health hazard.

The boundaries for ecotoxicity of Ni^{2+} compounds depend on whether they are Ni^{2+} salts, Ni^{2+} chelates, or organonickel compounds. There is also a molecular weight boundary for strong ion pairs/complexes which is 1000.

The boundaries for organonickel compounds (e.g., K_{ow} of the organic portion) are undefined but the molecular weight boundary is expected to be 1000.

Occupational Exposure Controls. Because nickel compounds have been shown to be toxic by the inhalation/ingestion route, exposure controls that maintain airborne exposures at 0.1 mg/m^3 or below are needed (consistent with OSHA PEL TWA). In addition, since nickel compounds are also toxic by the dermal route, NIOSH approved protective gloves are also recommended.

Testing. Depending upon estimated workplace exposures and releases to water, which will be assessed on a case-by-case basis, the following testing may be recommended:

To address health effects concerns due to the toxicity of nickel and its compounds, the following tests may be recommended:

A 90-day subchronic study in rats by an appropriate route to assess systemic toxicity (OPPTS 870.3100 or 870.3250 or 870.3465)

Results of the 90-day study may trigger a lifetime bioassay in rats and mice by the inhalation route to assess potential carcinogenicity (OPPTS 870.4200)

To address ecotoxicity concerns due to toxicity of nickel and its compounds, the following base set tests may be recommended:

Acute fish toxicity test	OPPTS 850.1075
Acute daphnid toxicity test	OPPTS 850.1010
Green algae toxicity test	OPPTS 850.5400

All tests utilize measured concentrations.

To properly assess human and environmental toxicity or exposure, certain physico-chemical or environmental fate properties need to be measured:

Water solubility	OPPTS 830.7840 or 830.7860
Octanol/water partition coefficient (K_{ow})	OPPTS 830.7550 or 830.7560 or 830.7570
Vapor pressure	OPPTS 830.7950 or 830.8000
Melting point-melting range	OPPTS 830.7200
Boiling point	OPPTS 830.7220

In addition, aerobic biodegradation by one of the following methods:

CO_2 evolution	OPPTS 835.3110
Closed bottle	OPPTS 835.3110
Modified OECD screening	OPPTS 835.3110
Modified MITI (I)	OPPTS 835.3110
DOC die-away	OPPTS 835.3110
Manometric respirometry	OPPTS 835.3110

References.

IRIS access. # 1271 (09/30/87) Nickel, soluble salts.

OSHA PELs (1995-1996)

September 1996

Category: <u>Nonionic Surfactants</u> Environmental Toxicity

Definition. Any neutral structure having surfactant activity is considered a member of this category. Many of these surfactants have the following types of structure:

$$C_x - (-O - CH_2 - CH_2 -)_y - OH$$

$$C_x - (-O - CH_2 - CH_2 -)_y - O - C_z$$

Ethoxylate groups may be mixed with or be replaced by alcohol groups. Other neutral groups e.g. propoxylates, esters, halogens, may also be present.

Hazard Concerns. Acute aquatic toxicity increases exponentially with increases in the hydrophobic chain length when the number of ethoxy groups or the hydrophilic component is held constant. In addition, when the number of carbons in the hydrophobe are constant, toxicity decreases with an increasing number of ethoxylate groups. The aquatic toxicity of members of the category can be predicted by structure-activity relationship (SAR).

Boundaries. There are no established molecular weight boundaries for this category. Limits on chain length are inherent in the SARs.

Testing. To address ecotoxicity concerns, base set acute aquatic toxicity testing (algae: static method, daphnid and fish: flow-through method, all measured concentrations).

Tier 1. The <u>acute aquatic base set</u> of environmental toxicity tests will be recommended for aquatic exposures and the <u>terrestrial base set</u> of environmental toxicity tests (i.e., the early seeding growth test, the earthworm acute toxicity test and the soil microbial community bioassay) will be recommended for any terrestrial exposures.

Acute fish toxicity test	OPPTS 850.1075
Acute daphnid toxicity test	OPPTS 850.1010
Green algae toxicity test	OPPTS 850.5400
Early seedling growth test	OPPTS 850.4230
Earthworm acute toxicity test	OPPTS 850.6200
Soil microbial community bioassay	OPPTS 850.5100

Tier 2. If acute toxicity testing indicates a significant risk, then environmental fate testing in the form of <u>aerobic biodegradation testing</u> is recommended. Aerobic biodegradability can be determined using <u>one</u> of the following test guidelines:

CO_2 evolution	OPPTS 835.3110
Closed bottle	OPPTS 835.3110
Modified OECD screening	OPPTS 835.3110
Modified MITI (I)	OPPTS 835.3110
DOC die-away	OPPTS 835.3110
Manometric respirometry	OPPTS 835.3110

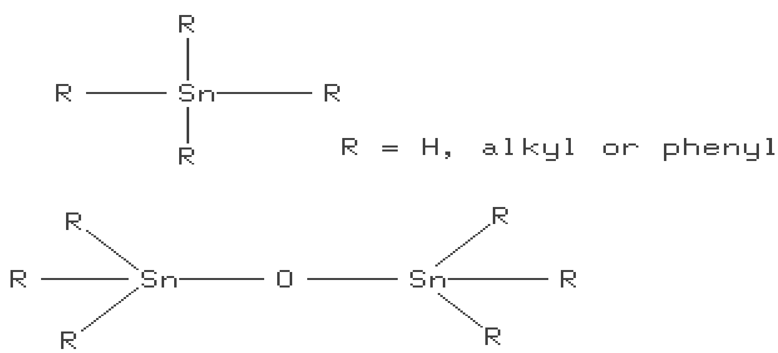
Tier 3. In addition, if acute toxicity testing indicates a significant risk, then chronic aquatic toxicity testing with fish and aquatic invertebrates will be recommended.

Fish early life stage test	OPPTS 850.1400
Daphnid chronic toxicity testing	OPPTS 850.1300

September 1988, revised September 1996

Category: Organotins Human Health Environmental Toxicity

Definition. This category includes all mono-, di-, tri- and tetra-alkyl or phenyl organotin compounds, including organotin esters/oxides. The mode of toxic action of organotins in humans is unknown, but they are known to affect carbonate metabolism and other metabolic processes in the brain, liver, and muscle, as well as several enzymes and the oxidative activity of mitochondria. It has been suggested that general sulfhydryl binding may be responsible for the effects seen in mammals. It is assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 and which do not transform to organotin compounds with MWs < 1000 will be excluded from this category. Human health and aquatic toxicity for liquid organotins is assumed to be limited by the relative octanol/water partition coefficient (a relative K_{ow} is based on the computer program, CLOGP, with C substituted for Sn). However, the limiting relative K_{ow} value is unknown. The Agency has data for an organotin with a relative log K_{ow} = 13.7 which still showed high toxicity towards fish and daphnids. Organotins which are solids at room temperature may show no toxicity at saturation at log K_{ow} values < 13.7 depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be observed at saturation. For solids, the no-effects-at-saturation determination has to be made on a case-by-case basis. There are no known K_{ow} limits for acute and chronic environmental toxicity at this time, but it is higher than a log K_{ow} = 13.7. Future testing will determine the K_{ow} limits.



Hazard Concerns. Tested organotins have been shown to be from moderately irritating to corrosive to the skin and eyes. Acute oral and dermal exposures can result in systemic effects, primarily neurotoxicity. Concerns for immunotoxicity are based on data on dialkyltins and trialkyltins. During a 13-week oral study in rats using dioctyltin bis (2-ethylhexylthioglycolate), effects to the thymus, spleen, lymph nodes, and bone marrow were observed. A No-Observable-Adverse-Effect-Level (NOAEL) of 1.6 mg/kg/d was derived from this study. During a 17-month feeding study in rats using bis (tri-n-butyltin)-oxide, immunoglobulin E (IgE) titers were reduced, as well as the activity of natural killer cells in the spleen, and there was reduced macrophage function. A NOAEL of 0.025 mg/kg/d was derived from this study. Based on the immunotoxicity end-point, an oral reference dose for chronic exposure (RfD) for tributyltin oxide of 3 x 10^{-5} mg/kg/d (IRIS 01/01/89) has been derived. Organotins are well known neurotoxins, with the tri- and tetra-substituted tins being more toxic than the mono- and di-substituted compounds. Although many tri-alkyltins show clear neurotoxic effects (eg. lesions in the hippocampus), the neurotoxic potential of di-alkyltins has not been as well defined. Available data indicate that dibutyltin and dioctyltin can produce neurotoxic effects such as reductions in brain neurotransmitter levels, alterations in spontaneous motor activity and hindlimb weakness. An effect level for neurochemical and behavioral changes following 3 days of oral administration of dibutyltin dilaurate was reported as 20 mg/kg. There are oncogenicity concerns for some of the organotins based on analogy to triphenyltin hydroxide, a group B probable human carcinogen. Therefore, the human health concerns for phenyltins will be dealt with on a case-by-case basis.

The acute aquatic toxicity for several subclasses of organotins has been determined through toxicity testing (Vighi & Calamari, 1985; Wong et al. 1982) and structure activity relationships (SAR). Organotins have been shown to be highly toxic to green algae (Wong et al. 1982). The acute toxicity of organotins is moderate to high towards daphnids (Vighi & Calamari, 1985). One datum for fish has indicated high toxicity (USEPA 1996). Organotins exhibit toxicity ranging from moderate toxicity (i.e., > 10 mg/L) to high toxicity (i.e., < 1 mg/L) depending on their K_{ow} , melting point, and MW. The higher the K_{ow}, the higher the toxicity (or the lower the EC_{50} value).

Boundaries. There are no known boundaries. The upper boundaries will be based on K_{ow} and MW. Acute toxicity expected with log $K_{ow} \leq 13.7$; chronic toxicity has no known upper bound for log K_{ow}, but it is ≥ 13.7. MW will be < 1000 for stable compounds. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures.

General Testing Strategy.

TIER 1.

A 90-day subchronic test in rodents by the oral route with special attention to the lymphoid organs (thymus, spleen, peripheral lymph nodes) and bone marrow (OPPTS 870.3100).

Neurotoxicity testing to include motor activity, a functional observational battery and neuropathology with special attention to lesions in the hippocampus (OPPTS 870.6200). This testing can be combined with the 90-day subchronic protocol cited above.

The acute aquatic base set of environmental toxicity tests will be recommended for aquatic exposures and the terrestrial base set of environmental toxicity tests will be recommended for terrestrial exposures. The acute toxicity tests for fish and daphnids should be done using the flow-through method with measured concentrations. Effective concentrations should be based on 100% active ingredients (AI) and mean measured concentrations. Measure TOC of dilution water in the control just prior to testing. Ideally, the highest treatment concentration on a mean measured concentration-basis should equal the aqueous solubility limit. Solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to significantly enhance the water solubility. The algal toxicity testing should be done with the static method and measured concentrations. Statistical analysis of effective concentrations at 24, 48, 72, and 96 hours should be performed. The test medium should be used with at least 0.300 mg/L EDTA as a final concentration.

<u>Aquatic Base Set</u>	
Acute fish toxicity test	OPPTS 850.1075
Acute daphnid toxicity test	OPPTS 850.1010
Green algae toxicity test	OPPTS 850.5400

<u>Terrestrial Base Set</u>	
Early seedling growth test	OPPTS 850.4230
Earthworm acute toxicity test	OPPTS 850.6200
Soil microbial community bioassay	OPPTS 850.5100

TIER 2.

If acute aquatic toxicity testing indicates a significant risk, the following environmental fate testing is recommended to determine <u>aerobic biodegradability</u> using <u>one</u> of the following test guidelines:

CO_2 evolution	OPPTS 835.3110
Closed bottle	OPPTS 835.3110
Modified OECD screening	OPPTS 835.3110
Modified MITI (I)	OPPTS 835.3110
DOC die-away	OPPTS 835.3110
Manometric respirometry	OPPTS 835.3110

TIER 3.

If acute toxicity testing and environmental fate testing continue to indicate a significant risk, then <u>chronic aquatic toxicity</u> testing with fish and aquatic invertebrates is recommended with flow-through methods and measured concentrations. Effective concentrations should be based on 100% active ingredients (AI) and mean measured concentrations. Conduct statistical analysis of effective concentrations at days 7, 14, 21, and 28. Measure TOC of dilution water in the control just prior to testing. Ideally, the highest treatment concentration on a mean measured concentration-basis should be equal at the aqueous solubility limit. Solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to significantly enhance the water solubility. The 7-d fish early life stage (ELS) toxicity test cannot be substituted for the 28-d ELS toxicity test and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because Van Leeuwen et al. (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d

ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen).

Chronic Aquatic Toxicity	
Fish early life stage test	OPPTS 850.1400
Daphnid chronic toxicity testing	OPPTS 850.1300

References.

8E-594.

Tributyltin oxide. Bis-(tri-n-butyltin)-oxide. (1988, December). Gesellschaft Deutscher Chemiker - Advisory Committee on Existing Chemical of Environmental Relevance (BUA). BUA Report 36.

USEPA 1996. United States Environmental Protection Agency (1996). The Office of Pollution Prevention andToxics (OPPT) premanufacture notification (PMN) ECOTOX database: a confidential business information (CBI) collection of environmental toxicity data from new chemical submissions under Sec. 5 of the Toxic Substances Control Act (TSCA). Washington, DC: Environmental Effects Branch, Health and Environmental Review Division (7403), OPPT, USEPA. OPPT contact is V. Nabholz, 202-260-1271.

Van Leeuwen, C.J., Adema, D.M.M., & Hermens, J. (1990). Quantitative structure-activity relationships for fish early life stage toxicity. Aquatic Toxicology, 16, 321-334.

Vighi, M., & Calamari, D. (1985). QSARs for organotin compounds on Daphnia magna. Chemosphere, 14, 1925-1932.

WHO 1980. World Health Organization Environmental Health Criteria 15. Tin and organotin compounds: A preliminary review. Geneva: WHO pp. 59-62.

Wong, P.T.S., Chau, Y.K., Kramar, O., & Bengert, G.A. (1982). Structure-toxicity relationship of tin compounds on algae. Canadian Journal of Fisheries and Aquatic Sciences, 39, 483-488.

April 1991, revised September 1996

Category: <u>Peroxides</u>

Human Health (case-by-case)
Environmental Toxicity

Definition. Any molecular structure containing one or more of the following functional groups is considered to be a member of the class:

```
 |     |
-C-O-O-C-        dialkyl peroxide
 |     |

 |
-C-O-O-H         alkyl hydroperoxide
 |

 O
 ‖     |
-C-O-O-C-        peroxy ester
       |

 O     O
 ‖     ‖
-C-O-O-C-        diacyl peroxide

 O
 ‖
-C-O-O-H         peroxy acid
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The category of peroxides is a small one (<0.2% of all new chemicals). The "typical" peroxide in the new chemical program is a discrete (class I) chemical with a molecular weight of <500.

Hazard Concerns. EPA had previously identified hazard concerns for the possible carcinogenicity of new chemicals falling into the peroxide category based on available evidence. EPA has reviewed test data developed by the Society of the Plastics Industry (SPI) and others on the peroxide category of chemicals and concludes that available information does not support continued identification of peroxides as a new chemical category presenting concerns for possible carcinogenicity. EPA will continue to evaluate the potential health concerns for new chemical peroxides that are notified but, with this change, will not apply a category understanding as regards potential carcinogenicity. While the assessment of potential human health hazard concerns will be conducted on a case-by-case basis, this modification does not affect EPA's approach to environmental hazard concerns which will continue to be identified for members of this category.

Boundaries. There are no established boundary conditions for review of peroxides.

<u>General Testing Strategy</u>.

The New Chemicals Program considers the following tests to be appropriate to address ecotoxicity concerns for peroxides:

1. Base-set ecotoxicity testing to include fish (40 CFR 797.1400), daphnids (40 CFR 797.1300), and algae (40 CFR 797.1050).

2. Environmental fate testing including, as appropriate, melting point (40 CFR 796.1300) or boiling point (40 CFR 796.1220), water solubility (40 CFR 796.1840 or 796.1860), log K_{ow} (40 CFR 796.1550, 796.1570, or 796.1720), vapor pressure (40 CFR 796.1950), hydrolysis (40 CFR 796.3500), direct and indirect photolysis (40 CFR 796.3765), and aerobic biodegradation by any of the following test guidelines-

Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

September, 1988; revised June, 1994; revised April, 2001

Category: <u>Persistent, Bioaccumulative, and Toxic (PBT) Chemicals</u>

Health/Environmental Toxicity
Environmental Fate

Definition. PBT chemical substances possess characteristics of persistence (P) in the environment, accumulation in biological organisms (bioaccumulation (B)), and toxicity (T) that make them priority pollutants and potential risks to humans and ecosystems. Prominent examples of PBT chemical substances include the insecticide, DDT and polychlorinated biphenyls (PCBs). This PBT category includes the boundary conditions, such as fish bioconcentration/bioaccumulation factors and environmental persistence values, that would determine inclusion in (or exclusion from) the category, and standard hazard and fate tests to address P, B, and T concerns for the chemical substances fitting the category description. For background information and discussion of this PBT category, see http://www.epa.gov/oppt/newchems/pbtpolcy.htm, and the proposed (October 5, 1998; 63 FR 53417) and final (November 4, 1999; 64 FR 60194) "Category for Persistent, Bioaccumulative, and Toxic Chemical Substances" published in the US Federal Register.

Hazard Concerns. Generally, PBT chemical substances are chemical substances that partition to water, sediment or soil and are not removed at rates adequate to prevent their bioaccumulation in aquatic or terrestrial species, with the potential to pose a risk via food chain toxicity.

Boundaries. The following table summarizes specific identification criteria and associated process for use in evaluating new chemical PBT substances.

	NEW CHEMICALS PROGRAM PBT CATEGORY CRITERIA AND PROCESS	
	TSCA Section 5 Action	
	<u>5(e) Order/Significant New Use Rule (SNUR)</u> Exposure/release controls included in order; testing required	<u>Ban Pending Testing</u> Deny commercialization; testing results may justify removing chemical from "high risk concern"
Persistence (transformation half-life)	>2 months	>6 months
Bioaccumulation* (Fish BCF or BAF)	$\geq$1000	$\geq$5000
Toxicity	Develop toxicity data where necessary, based upon various factors, including concerns for P, B, other physical/chemical factors, and toxicity.	

*Chemicals must also meet criteria for MW (<1000) and cross-sectional diameter (<20Å, or <20 x 10^{-8} cm). BCF of 1000 and 5000 are equivalent to log Kow of 4.2 and 5, respectively.

General Testing Strategy

***Tier 1*. Based upon SAR and professional judgment, the Agency identifies a new chemical substance as a possible PBT chemical substance.**

Log Kow	Liquid chromatography (OPPTS 830.7570/OECD 117) or generator column (OPPTS 830.7560) method
Ready biodegradability	Ready biodegradability (OPPTS 835.3110/OECD 301) 6 methods (choose one, or an equivalent test): DOC Die-Away, CO_2 Evolution, Modified MITI (I), Closed Bottle, Modified OECD Screening, Manometric Respirometry *or* Sealed-vessel CO_2 production test (OPPTS 835.3120)
Hydrolysis in water (if, based upon SAR, susceptibility to hydrolysis is suspected)	OPPTS 835.2110 (OECD 111)
Results	If the measured log Kow is <4.2 or if the test chemical passes the ready biodegradability test (i.e., not persistent in the environment), no further PBT-related testing is required. If the measured log Kow is greater than or equal to 4.2 and the chemical does not pass the ready biodegradability test, the chemical would require tier 2 testing. If hydrolysis testing is conducted and results in a half-life of <60 days, further testing may not be needed, but the need for testing must be determined after consideration of factors specific to the case, such as physical/chemical properties, persistence and bioaccumulative qualities of hydrolysis products, and the nature of the expected releases.

Tier 2. **Biodegradability and Bioaccumulation**

Biodegradability	Shake-flask die-away test (OPPTS 835.3170) or an equivalent test.
Bioaccumulation	Fish bioconcentration test (OPPTS 850.1730/OECD 305), or an equivalent test). Measured BCF should be based on 100 percent active ingredient and measured concentration(s).
Results	If the measured biodegradation half-life is >60 days and measured BCF is >1000, tier 3 testing will be required. If only one condition is met, releases and exposure are further considered to determine if additional testing is required.

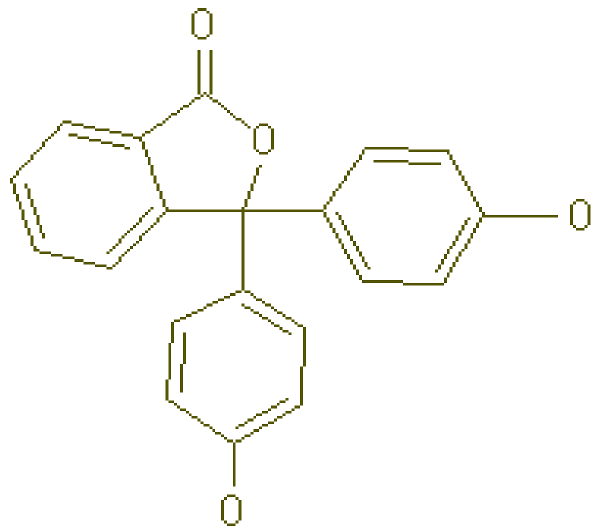
Tier 3. **Toxicity/advanced environmental fate testing.**

Human health toxicity	Combined repeated dose oral toxicity with the reproductive/developmental toxicity screening test (OECD No. 422) in rats. Other health testing will be considered where appropriate.
Environmental fate	Sediment/water microcosm biodegradation test (OPPTS 835.3180).
Chronic environmental toxicity	Fish (rainbow trout) and daphnids should be tested according to 40 CFR 797.1600 (same as OPPTS 850.1400/OECD 210) and 40 CFR 797.1330 (same as OPPTS 850.1300/OECD 202), respectively. Additional testing to evaluate other biota (e.g., avian, sediment dwelling organisms) or other effects (e.g., endocrine disrupting potential) will be considered where appropriate.

November, 1999

Category: <u>Phenolphthaleins</u> Human Health

Definition. Any chemical containing the phenolphthalein structure is considered to be a member of the category.



Hazard Concerns. The health concern for phenolphthalein and derivatives of phenolphthalein is for cancer based on the NTP cancer study (NTP report TR-465, November 1996) for phenolphthalein with administration via the diet. There was clear evidence of carcinogenic activity in male F344/N rats based on markedly increased incidences of benign pheochromocytomas of the adrenal medulla and of renal tubule adenomas and adenomas or carcinomas (combined). There was some evidence of carcinogenic activity in female F344/N rats based on the increased incidences of benign pheochromocytomas of the adrenal medulla in the 12,000 ppm group and of benign or malignant pheochromocytomas (combined) in the 12,000 and 25,000 ppm groups. There was clear evidence of carcinogenic activity in male $B6C3F_1$ mice based on increased incidences of histiocytic sarcomas and of malignant lymphomas of thymic origin. There was clear evidence of carcinogenic activity in female $B6C3F_1$ mice based on increased incidences of histiocytic sarcomas, malignant lymphomas of all types, lymphomas of thymic origin, and benign sex-cord stromal tumors of the ovary.

Boundaries. No boundaries currently defined.

Testing. EPA considers the following tests to be the most appropriate for phenolphthalein derivatives found to pose an unreasonable risk to human health:

Tier 1:

Comparative dermal and oral absorption study in rats (OPPT Harmonized Test Guidelines, 870.7485)

in vitro Chromosome aberrations study in Chinese hamster ovary cells with phenolphthalein as an additional positive control (OPPT Harmonized Test Guidelines, 870.5375)

Log Kow test (OPPTS 830.7550)

Water solublility for both lactone and acid form (OECD 105)

Ready biodegradability (OPPT 835.3110)

Tier 2:

2-year carcinogenicity study in mice (OPPT Harmonized Test Guidelines, 870.4200)

April, 1998

Category: Phenols Environmental Toxicity

Definition. This category includes phenols (i.e., monophenols), polyhydroxy phenols, and polyphenols. It is assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will be excluded from this category. Acute toxicity for phenols which are liquids at room temperature is known to be limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of about 7.38, phenols are expected to show no effects at saturation during 96-h exposures (Veith and Broderius 1987). Phenols which are solids at room temperature may show no toxicity at saturation at lower K_{ow} values depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be observed at saturation. For solids, no effects at saturation has to be demonstrated on a case-by-case basis. There are no known K_{ow} limits for chronic toxicity at this time, but it may not be much above a log K_{ow} = 9.0 for liquid phenols. Future testing will determine this K_{ow} limit.

Hazard Concerns. The acute and chronic toxicity for phenols can be predicted through SAR Analysis. SARs are available for fish 96-h LC50, daphnid 48-h LC50, green algal 96-h EC50, fish chronic value (ChV), daphnid ChV, and algal ChV. Members of this category exhibit toxicity ranging from low toxicity (i.e., > 100 mg/L) to high toxicity (i.e., < 1 mg/L) depending on their K_{ow}, MW, and substitutions (e.g., dinitrophenols).

Dinitrophenols are known to be more toxic than predicted by these SARs (see the category for polynitroaromatics).

Fate: Phenols are subject to indirect photolysis under environmentally realistic conditions.

Boundaries. There are no known lower boundaries. The upper boundaries will be based on K_{ow} and MW. Acute toxicity expected with log K_{ow} < 7.38; no effects at saturation during 96-h exposures when log K_{ow} >= 7.38. Chronic toxicity has no known upper bound for log K_{ow}, but it is probably near 9. MW will be < 1000. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log K_{ow} is >= 7.38, chronic toxicity testing with fish, daphnids, and green algae will be recommended.

General Testing Strategy

I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR 797.1400) and daphnids (40 CFR 797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should equal the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

The algal toxicity testing (40 CFR 797.1050), should be done with static methods; measured concentrations; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis equal to the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

If there is no significant risk from the PMN after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Direct and Indirect Photolysis Screening Test (40 CFR 796.3765). If $t½ \leq 2$ days, go to Tier 3; if $t½ > 2$ days, go to Tier 4.

Tier 3a. If $t½ \leq 2$ days and photolysis products are known and/or identified, then assess photolysis products for environmental hazards.

Tier 3b. If $t½ \leq 2$ days and photolysis products are not known and/or identifiable, then prepare a stock solution of PMN using the standard humic-containing solution described in the direct and indirect photolysis screening test [40.796.3765 (b)(2) and (c)(2)], expose to sunlight for at least 6 half-lives (t½), and test photolysis products for toxicity with most sensitive species from environmental base set. For example, the most sensitive species from the environmental base set has an EC50 value = 2.0 mg PMN/L (based on 100% AI, therefore, prepare a 5.0 mg PMN per liter stock solution based on 100% AI using the standard humic-containing solution. This stock solution is exposed to sunlight for at least 6 half-lives to ensure that all of the PMN has been photolyzed, and then this stock solution is used to retest the most sensitive aquatic species to determine if the photolysis products of the PMN are more or less toxic that the PMN.

Tier 4. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR 797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because Van Leeuwen et al (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen);

Daphnid chronic toxicity testing (40 CFR 797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test
because Van Leeuwen et al (1990) have demonstrated that the fish 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the fish 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen).

Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation	40 CFR 796.3100
Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

References.

Van Leeuwen CJ, Adema DMM, and Hermens J. 1990. Quantitative structure-activity relationships for fish early life stage toxicity. Aquatic Toxicology 16:321-334.

Veith GD and Broderius SJ. 1987. Structure-toxicity relationships for industrial chemicals causing type (II) narcosis syndrome. In Kaiser KLE (ed), QSAR In Environmental Toxicology - II, p 385-391. Reidel Publishing Company.

July, 1991

Category: <u>Phosphates, Inorganic</u>

Definition. This category includes all inorganic soluble forms of phosphates, such as, phosphoric acid [PO4H3 or OP(=O)(O)O] and its salts or phosphate salts, pyrophosphates, polyphosphates, and organic and inorganic forms of phosphorous that can be oxidized to phosphates rapidly. Inorganic forms of phosphonic acid (H2PO3 or OP(=O)O) are not included in this category because monopotassium phosphonic acid [13977-65-6] has been shown not to be an algal nutrient, not to be a replacement for phosphate in algal growth medium, and not to cause exponential growth of green algae.

Hazard Concerns. The standard environmental toxicity profile for inorganic phosphates as P in mg P/L is:

ECOTOX: Predicted (P) and measured (M) toxicity values in mg/L (ppm) are:
fish 96-h LC50 > 100.0 P
daphnid 48-h LC50 > 100.0 P
green algal 96-h EC50 b < 0.030 P
algal 96-h EC290 b = 0.030 M S,N
fish chronic value > 10.0 P
daphnid ChV > 10.0 P
algal ChV = 0.010 M Hutchinson 1957

Predictions are based on SAR-nearest analog analysis for soluble forms of inorganic phosphates (PO4); SAR chemical class = P-O4; MW of P = 31, PO4 = 95, PO4H3 = 98; pH7; effective concentrations based on 100% active ingredients and nominal concentrations of P; hardness <24.0 mg/L as CaCO3; and TOC <2.0 mg/L;
high concern for eutrophication;
assessment factor = 10.0
concern concentration = 0.001

Phosphate phosphorus has the potential to stimulate the growth of green algae and cause algal blooms and eutrophication in freshwater and marine environments. The phosphate anion is a plant nutrient and is the major limiting nutrient in many freshwater environments. The USEPA OW WQC (USEPA 1976) states:

[W]hen such concentrations [of total phosphate phosphorus]exceed 25 µg/l at the time of the spring turnover on a volume-weighted basis in lakes or reservoirs, they may occasionally stimulate excessive or nuisance growths of algae and other aquatic plants. Algal growths impart undesirable tastes and odors to water, interfere with water treatment, become aesthetically unpleasant and alter the chemistry of the water supply. The contribute to the phenomenon of cultural eutrophication.

To prevent the development of biological nuisances and to control accelerated or cultural eutrophication, total phosphates as phosphorus (P) should not exceed 50 µg/l in any stream at the point where it enters any lake or reservoir, nor 25 µg/l within the lake or reservoir. A desired goal for the prevention of plant nuisances in streams or other flowing waters not discharging directly to lakes or impoundments is 100 μg/l total P (Mackenthum, 1973). Most relatively uncontaminated lake districts are known to have surface waters that contain from 10 micrograms P/L (or 31 micrograms PO4H3/L) to 30 microg P/L (or 92 microg PO4H3/L) (Hutchinson, 1957).

Odum (1971) called phosphorus a major factor in the process of cultural eutrophication. Eutrophication results when nutrients, especially phosphates, are imported into aquatic ecosystems. This process is analogous to fertilizing an agricultural field. Phosphates act like a fertilizer and produce increases in the abundance of algae and other aquatic plants; eventually, they can result in excessive growths of algae (i.e., algal blooms). Excessive algae can block sunlight from reaching submerged macrophytes and other microalgae below the surface. When the algae die and fall to the bottom of slow-moving water or lakes, they are consumed by bacteria which use up available oxygen producing anaerobic conditions. Decaying algae cause odors and oxygen depletion of the water to occur with concomitant detriment to fish and aquatic invertebrates and, in turn, fishing and water-based recreational activities.

Phosphate concentrations as low as 0.050 mg P/L (ppm) or 50.0 micrograms P/L (ppb) will produce exponential growth of green algae in 96 hours (Miller et al. 1978), and phosphate concentrations from 10 to 60 micrograms P/L (ppb) were correlated to algal blooms and oxygen depletion (i.e., eutrophication) in Lake Washington, Seattle (Odum 1971). Phosphates have been severely limited or banned from detergents in 13 states, the District of Columbia, and several counties and municipalities (USEPA 1992). Sodium tripolyphosphate was one of the principal components of synthetic detergents. Freshwater green algae are clearly the most sensitive group of aquatic organisms to phosphate additions to water.

Boundaries. The boundaries for inorganic phosphate compounds depend on the release of inorganic phosphates which can be used by algae as a mineral nutrient. Any inorganic phosphate which can be used by algae as a nutrient or which transforms to release or becomes an algal nutrient is included in this category.

Testing. Based on a consideration of available data on inorganic phosphates and the physicochemical properties of these compounds, there is no need for further testing. However, if there is doubt about the availability of phosphate in a nutrient form from a PMN substance, then the algal toxicity test can be done with the PMN substance substituted for phosphate nutrient in the algal growth medium. If a PMN substance is capable of stimulating exponential growth green algae, it must be emphasized that inorganic phosphates should not be released to water because of their potential to cause eutrophication and their persistence.

Regulatory Actions.

(1) Phosphates have been severely limited or banned from detergents in 13 states, the District of Columbia, and several counties and municipalities (USEPA 1992).

(2) Water Quality Criterion, 1976 (USEPA 1976): total phosphates as phosphorus (P) should not exceed 50 micrograms p/L in any stream at the point where it enters any lake or reservoir, nor 25 micrograms P/L within the lake or reservoir.

(3) Hazard assessments of selected aqueous cleaner chemicals, USEPA (1990): OPPT recommendation to the Office of Air and Radiation: "...phosphates should never be released to water."

(4) Agency recommendation for a "nationwide elimination of the use of household laundry detergents containing phosphates." (USEPA 1992).

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March, 2000

Phosphinate esters are a class of organic compounds characterized by the functional group R-O-P(=O)(R)R. Phosphinate esters are metabolically active and exhibit excess aquatic toxicity in addition to narcosis. Phosphinate esters exhibit excess toxicity relative to simple esters (-C(=O)O-) and phosphate esters (-OP(=O)(O-)O-.

It is assumed that phosphinate esters need to be absorbed to be toxic, therefore, phosphinate esters with MW >1000 will be excluded from this category. Acute toxicity for phosphinate esters is known to be correlated and limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of >5.0, phosphinate esters show no effects at saturation during 96-hr exposures to fish. Phosphinate esters which are solids at room temperature may show no toxicity at saturation at lower K_{ow} values depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be observed at saturation. For solids, the no effects at saturation has to be determined on a case-by-case basis. There are no measured upper K_{ow} limits for chronic toxicity at this time, but it may not be much above a log K_{ow} = 8. Future testing will determine K_{ow} limits.

Hazard Concerns.

The toxicity for phosphinate esters has been determined through SAR analysis. SARs for freshwater species:

log fish 96-h LC_{50} (millimoles/L) = -1.201 -0.260 log K_{ow}
where n=2, R^2=1.0, LOGKOW (SRC)<5, MW<1000;

log daphnid 48-h LC_{50} (millimoles/L) = -1.501 -0.260 log K_{ow} where n=2, R^2=1.0, LOGKOW (SRC)<5, MW<1000;

log green algal 96-h EC_{50} (mmol/L) = -1.974 -0.332 log K_{ow}
where n=2, R^2=1.0, LOGKOW(SRC)<6.4, MW<1000, based on test data for *Pseudomonas putida*;

log fish ChV (millimoles/L) = -2.210 -0.499 log K_{ow}
where n=2, R^2=1.0, LOGKOW(SRC)<8, MW<1000, based on F96÷ACR10;

log daphnid ChV (millimoles/L) = -2.445 -0.407 log K_{ow}
where n=2, R^2=1.0, LOGKOW(SRC)<8, MW<1000, based on D48÷ACR10; and

log algal ChV (mmol/L) = -3.315 -0.223 log K_{ow}
where n=2, R^2=1.0, LOGKOW(SRC)<8, MW<1000, based on test data for *Pseudomonas putida*.

SARs for saltwater species:

log fish 96-h LC_{50} (millimoles/L) = -1.160 -0.368 log K_{ow}

where n=2, R^2=1.0, LOGKOW(SRC)<5, MW<1000; and

log mysid 96-h LC_{50} (millimoles/L) = -2,019 -0.476 log K_{ow}
where n=2, R^2=1.0, LOGKOW(SRC)<5, MW<1000.

Fate.

Phosphinate esters hydrolyze in water and their rate of hydrolysis is correlated with pH: the more alkaline the faster the hydrolysis. The SAR for hydrolysis is:

log hydrolysis t½ (d) = 4.325 -0.497 pH
where n=2, R^2=1.0.

At pH 7.1, the hydrolysis t½ = 6.3 days or 150 hours.

Boundaries.

MW <1000. Log K_{ow} <5.0 for acute toxicity to fish and aquatic invertebrates; log K_{ow} <6.4 for toxicity to green algae as a 96-h EC_{50}; and log K_{ow} assumed to be <8.0 for chronic toxicity to aquatic organisms, but could be higher.

General Testing Strategy. I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (OPPTS 850.1075) and daphnids (OPPTS 850.1010) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (ai) and mean measured concentrations; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; and solvent can be used to assist the aldehyde to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the test chemical significantly above its aqueous solubility limit.

The algal toxicity testing (OPPTS 850.5400), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (ai) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; and solvent can be used to assist the aldehyde to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the test chemical significantly above its aqueous solubility limit.

If there is no significant risk from the PMN chemical after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Aerobic biodegradability according to either of the following test guidelines:

Ready Biodegradability	OPPTS 835.3110
Sealed Vessel CO2 Production Test	OPPTS 835.3120

If there is no significant risk from the PMN chemical after the results of biodegradation testing have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 3.

Tier 3. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (OPPTS 850.1400), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN significantly above its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because the 7-d ELS toxicity test may underestimate chronic toxicity measured by the 28-d ELS toxicity test when the Chronic Values are compared.

Daphnid chronic toxicity testing (OPPTS 850.1300), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN significantly above its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because the daphnid 7-d short-term chronic toxicity test may underestimate chronic toxicity measured by the daphnid 21-d chronic toxicity test when the chronic values are compared.

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test [OPPTS 850.4230], the earthworm toxicity test [OPPTS 850.6200], and the soil microbial community bioassay [OPPTS 850.5100]) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

September 1996.

Definition.

There are two subcategories of polymers that are of concern:

- polyaromatic sulfonates - condensation products of sulfonated aromatics with formaldehyde, and

- polyacrylates with free carboxyl groups.

This category includes monomers with two or more acid groups and which act like organic acid chelators. The acid groups may include carboxylic acids, silicic acids, phosphoric acid, and sulfuric acids. These acids may also contain thiol substitutions. The acid groups on a monomer may be all of the same type of acid or may be a mixture of acids. The monomeric nucleus may include carbon, silica, oxygen, sulfur, and nitrogen, or mixtures of these elements. Members of this category must be water soluble or water self-dispersing. Molecular weights can be > 1000.

Hazard Concerns. Polyaromatic sulfonates are moderately toxic to fish, daphnids, and algae. The polyacrylates are toxic to algae only. There is no apparent relationship between charge density and toxicity, and no QSAR (quantitative structure-activity relationship) has been developed for these polymers, or the polyanionic monomers. Polyanionic monomers (as salts, e.g., Na or K salts) are moderately toxic to green algae, but show low toxicity to fish and daphnids. It is assumed that the toxicity of these compounds is due to over-chelation of nutrient elements needed for algal growth and that this toxicity will be mitigated in the presence of Ca^{++} either added to the compound before testing or present in the growth/test medium at a hardness of about 150 mg/L as $CaCO_3$.

Boundaries. Polymers must be water-soluble. Molecular weights are generally >1,000.

General Testing Strategy

To address ecotoxicity concerns, for polycarboxylic acids (polyacrylates) and polyanionic monomers, algal testing (static methods, nominal concentrations) is recommended, in 3 separate tests: 1) the test substance as is, 2) with equivalent of calcium ion, and 3) with growth medium at 150 mg/L hardness, as $CaCO_3$). For polyaromatic sulfonates, base set aquatic toxicity testing (flow through methods, measured concentrations) in algae, daphnids, and fish is recommended.

September, 1988; revised April, 1991

Category: Polycationic Polymers Environmental Toxicity

Definition. Any polymer that exists in the environment with multiple positive charges is a member of this class. Such structures include polyamines, polyquaternary ammonium, polysulfonium, and polyphosphonium compounds.

Hazard Concerns. Members of the category are toxic to fish, invertebrates, and algae. Algae are six-fold more sensitive than fish and daphnids. It is presumed that these compounds act on the surface of organisms and need not be absorbed. Toxicity increases exponentially with increasing charge density at cationic equivalent weights of >400. At lower charge equivalent weights, toxicity does not increase. A number of QSARs (quantitative structure-activity relationships) have been developed to predict the toxicity of polycationic polymers.

Boundaries. Polymers must be water-soluble or water-dispersible. Molecular weights are >300 although the typical new chemical polycationic polymer has a molecular weight in excess of 1000. EPA has been engaged in discussions with the Cationic Flocculant Producers Association in an attempt to identify and develop a set of tests on representative polycationic polymers which could better define the limits of the category.

General Testing Strategy

To address ecotoxicity concerns, for polymers with % amine nitrogen <0.7% and >0.1%: base set acute aquatic toxicity testing in algae, daphnids, and fish, plus humic acid testing in fish (20 mg/L humic acid in dilution water and 10 mg/L) is recommended. All testing uses static method, nominal concentrations. For some members of the class, a test of sorbed chemical using a benthic organism may also be recommended.

September, 1988; periodically revised.

Category: <u>Polynitroaromatics</u> Environmental Toxicity

This category includes all dinitroaromatics and trinitroaromatic compounds, for example, dinitrobenzenes, dinitroanilines, dinitrophenols, and dinitropyridines. Polynitroaromatics probably act by uncoupling of oxidative phosphorylation (Doull et al 1980). It is assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will be excluded from this category. Acute toxicity for polynitroaromatics which are liquids at room temperature is assumed to be limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of => 7.00 (based on test data for anilines reported Veith and Broderius 1987), polynitroaromatics are not expected to show toxic effects at saturation during 96-h exposures. Polynitroaromatics which are solids at room temperature may show no toxicity at saturation at lower K_{ow} values depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be observed at saturation. For solids, the no effects at saturation has to be determined on a case-by-case basis. There are no known K_{ow} limits for chronic toxicity at this time, but it may not be much above a log K_{ow} = 10 for liquid polynitroaromatics. Future testing will determine this K_{ow} limit.

Hazard Concerns. The acute and chronic toxicity for several classes of polynitroaromatics have been determined through SAR Analysis:

<u>dinitroanilines</u>:

fish 96-h LC50 (mM/L)= -0.027 -0.596 log K_{ow}; N=2; R^2=1.0
daphnid 48-h LC50 (mM/L)= -0.296 -0.558 log K_{ow}; N=2; R^2=1.0
fish ChV (mM/L)= -0.91 -0.661 log K_{ow}; N=2; R^2=1.0

<u>dinitrobenzenes</u>:

fish 96-h LC50 (mM/L)= -1.867 -0.333 log K_{ow}; N=2; R^2=1.0
daphnid 48-h LC50 (mM/L)= -0.325 -0.634 log K_{ow}; N=3;
R^2=0.86
fish ChV (mM/L)= -3.0 -0.40 log K_{ow}; N=2; R^2=1.0
daphnid ChV (mM/L) = -0.7 -0.625 log K_{ow}; N=2; R^2=1.0

<u>dinitrophenols</u>:

fish 96-h LC50 (mM/L)= -0.285 -0.559 log K_{ow}; N=4; R^2=0.96
daphnid 48-h LC50 (mM/L)= 0.083 -0.632 log K_{ow}; N=7;
R^2=0.85
fish ChV (mM/L)= -1.78 -0.552 log K_{ow}; N=4; R^2=1.0
daphnid ChV (mM/L) = -0.465 -0.654 log K_{ow}; N=2; R^2=1.0

Polynitroaromatics are known to be more toxic than predicted by the neutral organic SARs.

Members of this category exhibit toxicity ranging from low toxicity (i.e., > 100 mg/L) to high toxicity (i.e., < 1 mg/L) depending on their K_{ow} and MW.

Fate: Polynitroaromatics are expected to be subject to rapid direct and indirect photolysis under environmentally realistic conditions.

Boundaries.: There are no known lower boundaries. The upper boundaries will be based on K_{ow} and MW. Acute toxicity expected with log K_{ow} < 7.0; no effects at saturation during 96-h exposures when log K_{ow} >= 7.0. Chronic toxicity has no known upper bound for log K_{ow}, but it is probably near 10. MW will be < 1000. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log K_{ow} is >= 7.0, chronic toxicity testing with fish and daphnids will be recommended.

General Testing Strategy.

I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR 797.1400) and daphnids (40 CFR 797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should equal the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

The algal toxicity testing (40 CFR 797.1050), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis equal to the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

If there is no significant risk from the PMN after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Direct and Indirect Photolysis Screening Test (40 CFR 796.3765). If $t_{1/2} \leq 2$ days, go to Tier 3; if $t_{1/2} > 2$ days, go to Tier 4.

Tier 3a. If t½ ≤ 2 days and photolysis products are known and/or identified, then assess photolysis products for environmental hazards.

Tier 3b. If t½ ≤ 2 days and photolysis products are not known and/or identifiable, then prepare a stock solution of PMN using the standard humic-containing solution described in the direct and indirect photolysis screening test [40.796.3765 (b)(2) and (c)(2)], expose to sunlight for at least 6 half-lives (t½), and test photolysis products for toxicity with most sensitive species from environmental base set. For example, if the most sensitive species from the environmental base set has an EC50 value = 2.0 mg PMN/L (based on 100% active ingredients [AI]), then prepare a 5.0 mg PMN per liter stock solution based on 100% AI using the standard humic-containing solution. This stock solution is exposed to sunlight for at least 6 half-lives to ensure that all of the PMN has been photolyzed, and then this stock solution is used to retest the most sensitive aquatic species to determine if the photolysis products of the PMN are more or less toxic that the PMN.

Tier 4. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR 797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because Van Leeuwen et al (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen);

Daphnid chronic toxicity testing (40 CFR 797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because Van Leeuwen et al (1990) have demonstrated that the fish 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the fish 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen).

Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation	40 CFR 796.3100
Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

References.

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May, 1991

Category: Respirable, Poorly Soluble Particulates **Health Only**

Definition. This category includes a variety of inorganic, poorly soluble (as designated in ILSI 2000) particulates. Typically, they are oxides of various metals or nonmetals (i.e., silicon)

Boundaries. Potential for respirability--that is, if there are any particles $\leq 10\ \mu$ in diameter in the material being handled by workers. Summarized below are currently available test data on five different poorly soluble particulates–silica, talc, titanium dioxide, PMN 96-175 (lithium manganese oxide), and carbon black. The suitability of one or more of these analogues for a particular PMN particulate must be determined on a case-by-case basis. Risk is to be assessed by the margin of exposure method for the reason stated in the next paragraph.

Hazard Concerns

The category concerns discussed here are limited to effects on the lung as a result of inhaling the particles. Broadly, as shown in rat inhalation studies, these effects range from inflammation to fibrosis to, potentially, cancer. Because it is still not known with certainty whether high lung burdens of poorly soluble particulates can lead to lung cancer in humans via mechanisms similar to those of the rat, in the absence of mechanistic data to the contrary, it must be assumed that the rat model can identify potential carcinogenic hazards to humans. Since the apparent responsiveness of the rat model at overload is dependent on coexistent chronic active inflammation and cell proliferation, at lower lung doses in which chronic active inflammation and cell proliferation are not present, no lung cancer hazard is anticipated (ILSI 2000).

Some of the particulates may contain metals, for example, chromium, that may present other and more imminent toxicities, depending on the bioavailability of the metal ions. Thus, the toxicities of the metal components of the particulates must also be assessed, and on a case-by-case basis.

Lung Toxicity of Five Poorly Soluble Particulates

1. Fibrogenicity/Carcinogenicity of Crystalline Silica

Humans. Based on "sufficient evidence" for the carcinogenicity of inhaled crystalline silica from occupational sources, the International Agency for Research on Cancer (IARC, 1997) has classified crystalline silica as a Group 1 carcinogen in humans. According to IARC, studies of the following populations provided the least-confounded examinations of an association between silica exposure and cancer risk: gold miners, stone industry workers, granite shed and quarry workers, crushed stone industry workers, diatomaceous earth industry workers, refractory brick workers, pottery workers, and cohorts of registered silicotics. Not all of these studies demonstrated excess cancer risks; but, in view of the large number of epidemiological studies undertaken and the wide range of populations and exposure circumstances, some nonuniformity of results would be expected. In some studies, increasing risk gradients have been observed in relation to dose surrogates--cumulative exposure, duration of exposure, or the presence of radiographically defined silicosis--and, in one instance, to peak intensity exposure. For these reasons, the IARC Working Group concluded that overall, the epidemiological findings support increased lung cancer risks from inhaled crystalline silica resulting from occupational exposure.

Animals. IARC (1997) has concluded that there is "sufficient evidence" in experimental animals for the carcinogenicity of crystalline silica. A number of studies (*rev.in*: IARC, 1997; Woo *et al.*, 1988; Holland, 1990) have demonstrated that, in addition to silicosis/fibrosis, pulmonary tumors are induced in rats exposed to quartz (Mini-U-Sil; a common form of crystalline silica) by inhalation, single intrapleural, intraperitoneal, and/or intratracheal administration. In a 24-month inhalation study in rats, the lowest tested dose of respirable crystalline silica particles to induce lung tumors **(Lowest Observed Adverse Effect Level, or LOAEL) was 0.74 mg/m^3**.

☛ **Note for Cases Using Silica as Primary Analogue:** For LOAEL doses, the Agency considers a Margin of Exposure (MOE) of 1,000 or greater as representing a low order of toxicity for health endpoints for which a threshold dose is deemed appropriate. In this instance, exposures would have to be reduced to 0.0007 mg/m^3 to achieve a MOE of 1,000, a concentration that is practically impossible to achieve. Because the LOAEL of 0.74 mg/m^3 is based on test data on pure silica and because silica is considered to be a much more potent lung toxicant than crystalline particulates containing silica, **the Agency has adopted the NIOSH REL (Recommended Exposure Level) for silica, 0.05 mg/m^3, as a NCEL1/ (New Chemical Exposure Limit - see http://www.epa.gov/oppt/newchems/ncelmain.htm for more information) concentration that would adequately protect workers from crystalline particulates containing silica. This NCEL replaces the former one based on OSHA Permissable Exposure Limit (PEL) for silica 0.1 mg/m^3.**

2. Fibrogenicity/Carcinogenicity of Talc

Humans. Epidemiology studies suggest an association between nonfibrous talc (a finely powdered hydrous magnesium silicate) and lung cancer risk. The OSHA PEL for talc is 20 mppcf (million particles per cubic foot), and the NIOSH-recommended 8-hr TWA concentration is 2 mg/m^3.

Animals. In an NTP inhalation study (NTP TR 421, 1993), male and female F344 rats were exposed to 0, 6, or 18 mg/m^3 talc for 113 and 122 weeks, respectively. There was clear evidence of the carcinogenicity of talc in female rats based on the increased incidence of alveolar/bronchiolar adenomas and carcinomas of the lung in the **18-mg/m^3 group (LOAEL).** The **No Observed Adverse Effect Level (NOAEL) from this study is 6 mg/m^3**. The NCEL for analogous particulates would be 0.06 mg/m^3.

3. Fibrogenicity/Carcinogenicity of Titanium Dioxide (TI)

Humans. According to IARC (ACGIH 1993), there is **inadequate evidence** for the carcinogenicity of TI in humans. [There is limited evidence for the carcinogenicity of TI in experimental animals.] Overall evaluation: TI is not classifiable as to its carcinogenicity to humans. The OSHA PEL's for nuisance dust (in which TI is included) are 15 mg/m^3 total particulates and 5 mg/m^3 respirable fraction. The ACGIH TLV-TWA is 10 mg/m^3 of total dust containing no asbestos and <1% crystalline silica.

The various literature case reports of lung toxicity in TI-exposed workers are generally inconclusive because of several factors--smoking; other conditions, such as tuberculosis; or incomplete data on TI exposure histories.

In one fairly comprehensive cohort study, Chen and Fayerweather (1988, as summarized in ACGIH 1993) analyzed lung cancer mortality and incidence of chronic respiratory disease, chest x-ray abnormality, and pulmonary fibrosis among 1,576 workers exposed to TI for at least 1 yr at two production facilities between 1935 and 1984. Of the 211 deaths, 14 were attributed to respiratory cancer and 11 to nonmalignant respiratory disease compared with 18.3 and 13.8 cases expected, respectively, based on US mortality data. Expected deaths based on company mortality data since 1957 were 16.6 from respiratory cancer and 8.3 from nonmalignant respiratory disease. The authors concluded that the increase in deaths from nonmalignant respiratory disease compared with company data was not statistically significant. They further concluded that there was no significant association between exposure to TI and the respiratory diseases studied.

Animals. There is limited evidence for the carcinogenicity of TI in experimental animals. Two-year inhalation studies in animals are summarized below.

(1) Lee et al. (1986, as cited in ACGIH 1993 and in USEPA 1983) exposed Charles River-CD rats to 0, 10, 50, or 250 mg/m^3 for 6 hr/day 5 days/wk for 2 yr. The mean respirable fractions were 93.7% or greater. Squamous cell carcinomas developed after exposure to the highest dose for the full 2 yr. The authors considered the carcinomas to be unique, experimentally induced tumors in rats and to be of questionable relevance to humans. Given the amount of dust in the rat lungs, the tumors were postulated to be the result of saturation of normal pulmonary clearance mechanisms. There were minute areas of lung fibrosis at the two higher exposure levels.

At 50 mg/m^3, massive accumulations of dust-laden macrophages, foamy dust cells, and free particles were considered indicative of such an overload. At 10 mg/m^3, the architecture of the air spaces remained intact and there was no significant formation of scar tissue. **The NOAEL is 10 mg/m^3.**

(2) Heinrich et al. (1995, abstract only) exposed Wistar rats to diesel engine exhaust, carbon black, or ultrafine TI for 2 yr. Particle exposure concentrations were increased during the course of the experiment. The average particle concentration of TI was 10 mg/m^3. Lung tumor rates (not given) increased with increasing cumulative particle exposure times, independent of the type of particle.

(3) Trochimowicz et al. (1988, abstract only) exposed Charles River-CD rats to 10, 50, or 250

mg/m^3 TI for 6 hr/day, 5 days/wk for 104 wk. Microscopic findings included alveolar cell hyperplasia, dust deposition, and minute areas of collagen fiber deposition associated with cholesterol giant cell granulomas. The earliest indicator of TI exposure was alveolar cell hyperplasia. Lung tumors were only found in rats exposed to 250 mg/m^3. The **NOAEL from this study is 10 mg/m^3.**

On the basis of the NOAEL's from the above studies, the NCEL for analogous particulates would be 0.1 mg/m^3. However, this would make the NCEL for TI analogues identical to that for silica, a highly potent lung toxicant that IARC (1997) has classified as a Group 1 carcinogen in humans (see section 1, above). Therefore, it was decided to use the OSHA PEL for TI, which is 5 mg/m^3 (respirable fraction), as the NCEL for TI analogues.

4. Lung Toxicity of PMN 96-175, Lithium Manganese Oxide

Animal Data Only. Rats were exposed by inhalation to 0 (air controls), 1, 4, or 16 mg/m^3 of the PMN substance 6 hr/day, 5 days/wk for 90 days. At the highest concentration, rats developed inflammation of the lung and larynx. Similar results were seen in the 14-day range-finding study at concentrations ranging from 10 to 100 mg/m^3. The **NOAEL from this study is 4 mg/m^3.** The NCEL for analogous particulates would be 0.04 mg/m^3.

5. Fibrogenicity/Carcinogenicity of Carbon Black

Chronic inhalation of carbon black produced pulmonary inflammation, fibrosis, and lung tumors in rats (Nikula et al. 1995, Heinrich et al. 1995). These effects were observed at dust concentrations of 2.5, 6.6, and approximately 10 mg/m^3 carbon black. The **LOAEL from these studies is 2.5 mg/m^3.** The NCEL for analogous particulates would be 0.0025 mg/m^3. [The OSHA PEL for carbon black is 3.5 mg/m^3.]

General Testing Strategy

A 90-day inhalation toxicity test (CFR 870.3465) in rats with special attention to histopathology (inflammation and cell proliferation) of the lung tissues and to various parameters of the bronchoalveolar lavage fluid (BALF), e.g., marker enzyme activities, total protein content, total cell count, cell differential, and cell viability. It is not necessary to look at internal organs. It is recommended that a recovery period of 60 days be included to assess the progression or regression of any lesions. If the results of the subchronic study indicate that the PMN particles have carcinogenic potential, a 2-year inhalation bioassay in rats may be warranted.

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Woo, Y.-T., Lai, D.Y., Arcos, J.C., and Argus, M.F.: Chemical Induction of Cancer, Vol. III C, Academic Press, p. 508, 1988.

October, 2002

This category includes rosin, abietic acid, abietinic acid, sylvic acid, their salts, and polymeric forms whose MW < 1000. The mode of toxic action of rosin is unknown. It is assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will be excluded from this category. It is also assumed that these compounds need to be water soluble to be toxic, therefore, compounds with water solubilities (WS) < 0.001 mg/L (ppm) will also be excluded from this category.

Hazard Concerns. The acute toxicity for rosin towards fish has been measured to be between 0.410 to 0.700 mg/L by Leach and Thakore (1976 and 1978). Toxicity to aquatic invertebrates and green algae have no been reported. Based on these data, rosin presents a high concern for toxicity towards the aquatic environment.

Boundaries. The only lower boundary is water solubility which is set at 0.001 mg/L (ppm). The only upper boundary will be set at a MW $\geq$ 1000 for stable compounds. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures.

General Testing Strategy.

The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (CFR §797.1400) and daphnids (CFR §797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should equal the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility.

The algal toxicity testing (CFR §797.1050), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis equal to the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility.

Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (CFR §797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because Van Leeuwen et al

(1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen);

Daphnid chronic toxicity testing (CFR §797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because Van Leeuwen et al (1990) have demonstrated that the fish 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the fish 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen).

The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test [§797.2800], the earthworm acute toxicity test [§795.150], and the soil microbial community bioassay [795.3700]) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test [§797.2830], the plant uptake test [§797.2850], and the soil microbial community bioassay.

References.

Leach , J. M. and Thakore, A. N., 1976. Toxic constituent in mechanical pulping effluents. Tappi, 59:129.

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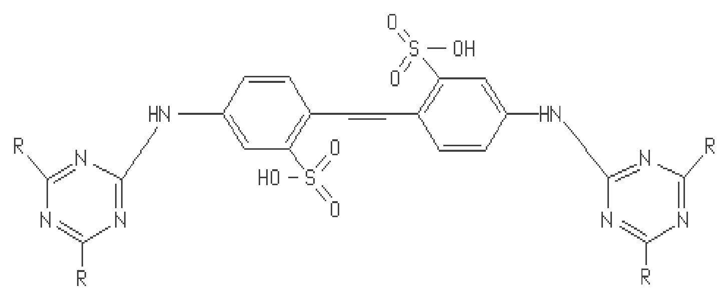
Van Leeuwen CJ, Adema DMM, and Hermens J. 1990. Quantitative structure-activity relationships for fish early life stage toxicity. Aquatic Toxicology 16:321-334.

January, 1994

Category: **<u>Stilbene, derivatives of 4,4-bis(triazin-2-ylamino)-</u>**

Human Health (case-by-case)

Definition. Any water soluble (sulfonated) derivative of 4,4-bis(triazin-2-ylamino) stilbene is considered to be a member of this category.



Hazard Concerns. EPA previously identified hazard concerns for the possible developmental/reproductive toxicity of new chemicals falling into this stilbene, derivatives of 4,4-bis(triazin-2-ylamino)- category based on published test results for a member of the category. EPA has reviewed test data developed by the Stilbene Whitening Agent Task Force of the Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers (ETAD). These studies consisted of a range-finding and definitive 2-generation rat study (gavage) and range-finding and definitive developmental toxicity studies in rats and rabbits (gavage) for C.I. Fluorescent Brightener 220 (CAS No. 16470-24-9). Based on the results from these studies, EPA has concluded that available information does not support continued identification of stilbenes as a new chemical category presenting concerns for possible developmental/reproductive toxicity. EPA will continue to evaluate the potential health concerns for new chemical stilbenes that are notified but, with this change, will not apply a category understanding as regards potential developmental/reproductive toxicity.

References.

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Turck, PA. Range-finding reproduction study of C.I. Fluorescent Brightener 220 administered via oral gavage to rats. MPI Research Laboratory Study Identification 795-005, June 8, 2000a.

Turck, PA. Prenatal developmental toxicity study of C.I. Fluorescent Brightener 220 administered via oral gavage to New Zealand White rabbits. MPI Research Laboratory Study Identification 795-004, January 27, 2000b.

Turck, PA. Two generation reproduction and fertility study of C.I. Fluorescent Brightener 220 administered via oral gavage in rats. MPI Research Laboratory Study Identification No. 795-006, August 24, 2001.

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8E-CAP - 0024. Report to Ciba-Geigy Corporation. Teratogenic study with FA-15 in Albino rabbits, May 23, 1972. Submitted to USEPA on October 9, 1992.

PB81-148819. Information Hazard Profiles on Potential Occupational Hazards. Vol. 2. Chemical Classes Fluorescent Whitening Agent (FWA's). National Institute for Occupational Safety and Hazard, Rockville, Maryland. December 1979.

January, 1992; revised December, 1994; revised August, 2002.

This category includes all thiols or mercaptans. It is assumed that thiols have to be absorbed to be toxic, therefore, compounds with MWs > 1000 will be excluded from this category. Acute toxicity for thiols which are liquids at room temperature is known to be limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of <6.5 (CLOGP), thiols show no effects at saturation during 96-h exposures. Thiols which are solids at room temperature may show no toxicity at saturation at lower K_{ow} values depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be observed at saturation. For solids, the no effects at saturation has to be determined on a case-by-case basis. There are no known K_{ow} limits for chronic toxicity at this time, but it may not be much above a log K_{ow} of 8 to 9 for liquid thiols. Future testing will determine this K_{ow} limit.

Hazard Concerns. The acute toxicity for thiols has been determined through SAR Analysis:

fish 96-h LC50 (millimoles/L) = -1.022 - 0.447 log K_{ow}
daphnid 48-h LC50 (millimoles/L) = -3.2 - 0.097 log K_{ow}

Effective concentrations for green algal 96-h EC50 should be assumed to be similar to fish and daphnids.

Thiols which are substituted with a carboxylic acid will be about 10 times less toxic than predicted by this SAR at pH 7. Use the K_{ow} for the free acid.

Members of this category exhibit toxicity ranging from low toxicity (i.e., > 100 mg/L) to high toxicity (i.e., < 1 mg/L) depending on their K_{ow}, MW and substitutions.

Boundaries. There are no known lower boundaries. The upper boundaries will be based on K_{ow} and MW. Acute toxicity expected with log K_{ow} <6.5; no effects at saturation during 96-h exposures when log K_{ow} $\geq$6.5. Chronic toxicity has no known upper bound for log K_{ow}, but it is probably near 9. MW will be <1000. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log K_{ow} is $\geq$6.5, chronic toxicity testing will be recommended.

General Testing Strategy

I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (CFR §797.1400) and daphnids (CFR §797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should equal the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

The algal toxicity testing (CFR §797.1050), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis equal to the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

If there is no significant risk from the PMN after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation	40 CFR 796.3100
Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

If there is no significant risk from the PMN after the results of the aerobic biodegradation have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 3.

Tier 3. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (CFR §797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test.

Daphnid chronic toxicity testing (CFR §797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test.

II. <u>Release to Terrestrial Ecosystems</u>

The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

December, 1994

This category includes substituted triazines which can be aromatic, partially aromatic (or partially saturated) and unsaturated. The nitrogens in the triazine ring may be symmetrical or asymmetrical. Substitutions on the carbons may include but not be limited to: aliphatic alcohols; ketones; benzene and substituted benzenes; aliphatic hydrocarbons, alkyenes and alkynes; free amines and substituted amines; cyclic aliphatic hydrocarbons; halogens; amides; cyanides; ethers; methoxy groups; sulfides; azido groups; and carboxylic acid esters. Substitutions on the nitrogens may include but not be limited to: free amines and substituted amines; -N=CH; aliphatic hydrocarbons, alkyenes and alkynes; and benzene and substituted benzenes.

Hazard Concerns. Many members of this category are commercial herbicides which are used to control both aquatic plants and terrestrial plants. Their mode of toxic action is generally considered to be inhibition of photosynthesis. Many members of this class are toxic to algae at < 1 mg/L and toxic to terrestrial vascular plants at < 1 mg/kg. Members of this group can also be highly toxic to fish and aquatic invertebrates. Toxicity is expected to be related to the octanol/water partition coefficient with respect to fish and aquatic invertebrates, but toxicity to plants may not be related to Kow when log Kow < 5. When the log Kow is < 5, algae and terrestrial plants are expected to be the most sensitive species. As log Kow increases, species differences are expected to diminish. At this time there is no formalized SAR for this category for any species. Toxicity predictions will be made using either the closest analog or averaging data for the two closest analogs which bracket the chemical under question.

Boundaries. There are no known lower boundaries. The upper boundaries are based on Kow and MW. When the log Kow value is < 5 mg/L, the environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log Kow is between 5 and 8, only chronic toxicity testing will be recommended. When the log Kow is > 8, no testing will be requested because no toxic effects at saturation will be expected. Generally, members of this category will have MWs of less than 1000.

<u>General Testing Strategy</u>

The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures and the terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm acute toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures.

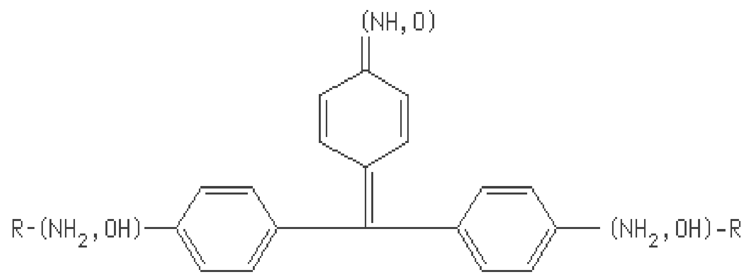
August, 1989

Category: <u>Triarylmethane Pigments/Dyes with Non-solubilizing Groups</u>

Human Health
Environmental Toxicity

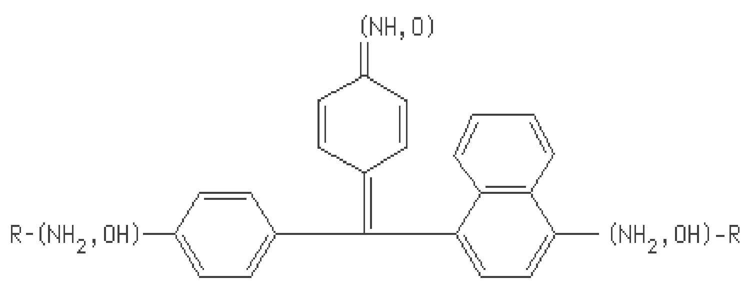
Other Names: Triphenylmethane Pigments/Dyes, Diphenylnaphthylmethane Pigments/Dyes

Definition. Structurally, triarylmethane pigments/dyes are derivatives of triphenylmethane or diphenylnaphthylmethane. In order to achieve the required spectral absorption properties that characterize these dyes, amine groups (primary, secondary, or tertiary) or hydroxyl groups must be present on the aromatic ring positions para to the methane carbon. Amine substitutions are more prevalent than hydroxy substitutions (C.I. 42000-42175 for diamino derivatives, C.I. 42500-42800 for triamino derivatives, C.I. 43800-43875 for hydroxy derivatives, and 43500-43570 for aminohydroxy derivatives).



triphenylmethane

R = CH3,C2H5



diphenylnaphthylmethane

R = CH3,C2H5

Hazard Concerns. There are oncogenicity concerns for the triarylmethane pigments/dyes based on analogy to Gentian Violet and C.I. Basic Red 9. In addition, there are developmental and reproductive toxicity concerns for these compounds based on analogy to Gentian Violet and Malachite Green. Ecotoxicity concerns are based on QSAR predictions for delocalized cationic dyes. Cationic dyes are an established ecotoxicity category.

Boundaries. Pigments/Dyes included in this category are the di- and tri-amino substituted triphenylmethane and diphenylnaphthyl-methane derivatives. Dyes substituted with solubilizing groups such as carboxylic acid, sulfonic acid, or halogens, are not included. Pigments that have essentially negligible water solubility (<1ppb) and therefore, little or no bioavailability, are also not included.

General Testing Strategy

The New Chemicals Program considers the following tests to be appropriate to address the potential for triarylmethane pigments/dyes to pose a significant risk.

For Health -

1. Developmental toxicity study in two species of rodents by the oral route (40 CFR 798.4900).

2. Two-generation reproductive toxicity study in rodents by the oral route (40 CFR 798.4700).

3. Salmonella typhimurium/Ames assay with the Chinese hamster liver S9 activation system (40 CFR 798.5265).

4. In vivo mouse micronucleus assay i.p. (40 CFR 798.5395).

Tests 3. and 4. would trigger a lifetime rodent bioassay if positive.

For Environmental toxicity and fate -

Prior to Tier 1, the following physical-chemical properties need to be established:

Melting point (40 CFR 796.1300) or boiling point (40 CFR 796.1220), water solubility (40 CFR 796.1840), log K_{ow} (40 CFR 796.1550, 796.1570 or 796.1720), and vapor pressure (40 CFR 796.1950).

Tier 1. The fish, daphnid, and algal (40 CFR 797.1050) acute toxicity tests from the aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (CFR §797.1400) and daphnids (CFR §797.1300) will be done using the flow-through method with measured concentrations, and effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations.

If there is no significant risk from the PMN after the results of the fish and daphnid acute toxicity tests have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Direct and Indirect Photolysis Screening Test (40 CFR 796.3765). If $t½ \leq 2$ days, go to Tier 3; if $t½ > 2$ days, then integrate the results into the risk assessment. If there is no significant risk from the PMN, then no further testing is recommended. However, if there remains a significant risk, then go to Tier 4.

Tier 3a. If $t½ \leq 2$ days and photolysis products are known and/or identified, then assess photolysis products for environmental risk. If there is no significant risk from the photolysis products from the PMN, then no further testing is recommended. However, if there remains a significant risk, then go to Tier 4.

Tier 3b. If $t½ \leq 2$ days and photolysis products are not known and/or identifiable, then prepare a stock solution of PMN using the standard humic-containing solution described in the direct and indirect photolysis screening test [40.796.3765 (b)(2) and (c)(2)], expose to sunlight for at least 6 half-lives (t½), and test photolysis products for toxicity with most sensitive species from environmental base set. For example, if the most sensitive species from the environmental base set has an EC50 value = 2.0 mg PMN/L (based on 100% active ingredients [AI]), then prepare a 5.0 mg PMN per liter stock solution based on 100% AI using the standard humic-containing solution. This stock solution is exposed to sunlight for at least 6 half-lives to ensure that all of the PMN has been photolyzed, and then this stock solution is used to retest the most sensitive aquatic species to determine if the photolysis products of the PMN are more or less toxic that the PMN. Integrate these toxicity results into the risk assessment. If there is no significant risk from the PMN, then no further testing is recommended. However, if there remains a significant risk, then go to Tier 4.

Tier 4. Test for aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

Integrate the results for aerobic biodegradability into the risk assessment. If there is no significant risk from the PMN, then no further testing is recommended. However, if there remains a significant risk, then do chronic toxicity testing for fish and daphnids:

Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (CFR §797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; and statistical analysis of effective concentrations at days 7, 14, 21, and 28.

Daphnid chronic toxicity testing (CFR §797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21.

For Terrestrial ecosystems-

The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

References:

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July, 1994.

Category: Vinyl Esters

Human Health
Environmental Toxicity
(See "Esters")

Definition: A carboxylic acid ester with at least one vinyl group (CH_2=CH-) attached to an organic acid radical (RCOO-). A simple vinyl ester is vinyl acetate:

$$CH_3COOCH{=}CH_2$$

Note: Certain carboxylic acid moieties themselves may exert toxicity such that there are concerns for effects **in addition** to those identified for the vinyl ester class.

Hazard Concerns: Oncogenicity based on data from two bioassays: a 2-yr drinking water study of vinyl acetate in rats [significantly increased incidences of adenocarcinomas of the uterus and combined C-cell adenomas and carcinomas in high-dose (2,500 mg/l) female rats] and a chronic inhalation study of vinyl acetate in rats and mice (laryngeal/nasal tumors in rats, bronchiolar/alveolar adenomas in lungs of mice). There are supporting data from 27-mo and 81-wk inhalation studies of acetaldehyde in rats and hamsters, respectively. Furthermore, mutagenicity data on these analogues support a cancer concern. Neurotoxicity based on data on an analogous PMN compound in rats plus suggestive data on vinyl acetate. Reproductive toxicity based on a two-generation study of vinyl acetate in rats. Environmental toxicity (see "Esters" category).

Boundaries: Other than a requirement for a vinyl group and an acid group, none.

General Testing Strategy

(1) Up-front glove permeation study if there is a risk of any toxicity through dermal exposure.

(2) Hydrolysis test (both acid- and enzyme-catalyzed) to determine the rate at which acetaldehyde, a potentially toxic metabolite, is released. [The requirement to measure acetaldehyde release is based on the assumption that acetaldehyde is the presumed "ultimate carcinogen" of vinyl esters. This requirement will be revisited as more decisive data become available. The hydrolysis data should be helpful in determining the most appropriate route of administration in the following tests.]

(3) A 90-day neurotoxicity test in rats that includes a functional observational battery, motor activity tests, and neuropathology examinations. Also to be included, to address reproductive toxicity concerns, are the following adjuncts to the subchronic test:

(a) Weights of the testes, epididymides (total and cauda), pituitary, seminal vesicles (with coagulating glands), prostate, ovary, and uterus are to be recorded at the time of sacrifice.

(b) Histopathology of the testes is to be done on the males at the time of sacrifice. Particular attention is to be directed toward achieving satisfactory quality from fixation and embedding, and preparations are to follow the recommendations of Russell et al. (1990). Histologic analyses are to include evaluations of the spermatogenic cycle; i.e., the presence and integrity of the 14 cell states. These evaluations would follow the guidance provided by Russell et al.

(4) A standard developmental toxicity study in rabbits and rats.

(5) A 2-yr bioassay in rats and mice to address cancer concerns.

(6) Environmental toxicity testing: see "Esters" category.

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August, 1992

Category: <u>Vinyl Sulfones</u>

Human Health
Environmental Toxicity

Definition. Any molecular structure with a vinyl sulfone group is considered to be a member of the class:

$$-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-CH=CH_2$$

In addition the following is an example of a functional group that generates a vinyl sulfone under certain conditions. β-Sulfatoethyl-sulfonyl groups are typical vinyl sulfone precursors. Structures bearing this group are also members of the class:

$$-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-CH_2-CH_2-OSO_3^-$$

Typically, the new chemical of concern is a fiber-reactive dye bearing one or more vinyl sulfones, or vinyl sulfone precursors. Occupational exposure to workers via inhalation/ingestion of the powdered dye may pose a potential health risk. Under the conditions in a dye bath a vinyl sulfone precursor-containing dye generates the vinyl sulfone. In this scenario the only potential risk is to those who drink contaminated drinking water. However, following covalent binding of vinyl sulfone to textile fibers, survival of unbound vinyl sulfone substituents in the dye bath is low (< 10%). The majority of unbound vinyl sulfone is hydrolyzed to β-hydroxyethylsulfone. Unless releases to water are extremely high, vinyl sulfones are not expected to pose a significant risk to human health. Presently, there are no human health concerns for β-hydroxyethylsulfone.

Hazard Concerns. For those who inhale or ingest a vinyl sulfone, there is an oncogenicity concern and mutagenicity concerns based on the potent mutagenicity of vinyl sulfone (VS) and methylvinyl sulfone (MVS). VS and MVS are mutagenic in the L5178Y $TK^{+/-}$ mouse lymphoma gene mutation assay <u>in</u> <u>vitro</u>. Evaluation of small colonies indicates that genotoxicity is due to a clastogenic mechanism. This is confirmed by evaluating the lymphoma cells for chromosome aberrations and micronuclei. MVS also induces effects upon the spindle apparatus in Chinese hamster lung cells <u>in</u> <u>vitro</u>, indicating an aneugenic (aneuploidy-inducing) activity. A direct-acting Michael addition-type reaction may be the mechanism of action. Although MVS and divinyl sulfone (DVS) are both reported as negative <u>in</u> <u>vivo</u> in the mouse micronucleus assay (inconclusive, only males tested), and in the dominant lethal assay, the Agency has determined that these negatives are not sufficient to remove concern for vinyl sulfone-containing new chemicals as potential mutagens and carcinogens.

There are ecotoxicity concerns for VS only, based on concerns for electrophiles.

Boundaries. There are at present no boundary conditions, related to health effects, for structures containing vinyl sulfones. Nearly all new chemicals in the category have been water-soluble, fiber-reactive dyes with molecular weights <1,000. The boundary conditions for ecotoxicity effects are molecular weights < 1000 and log K_{ow} < 8.

General Testing Strategy

The New Chemicals Program considers the following tests to be appropriate to address health and ecotoxicity concerns:

1. Mouse lymphoma assay with evaluation of small colonies (40 CFR 798.5300). The test would trigger a lifetime rodent bioassay if positive.

2. Base-set ecotoxicity testing to include fish (40 CFR 797.1400), daphnids (40 CFR 797.1300) and algae (40 CFR 797.1050). The acute toxicity tests for fish and daphnids will be done using the flow-through method with measured concentrations, and effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations. If there is insufficient knowledge about the water solubility of the dye, then it should also be measured (40 CFR 796.1840 or 796.1860).

If there is no significant risk from the PMN after the results of the fish and daphnid acute toxicity and algal toxicity tests have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then do environmental fate testing as outlined in 3.

3. Environmental fate testing for releases to water.

Tier 1. Direct and Indirect Photolysis Screening Test (40 CFR 796.3765). If t½ ≤ 2 days, go to Tier 2; if t½ > 2 days, go to Tier 3.

Tier 2a. If t½ ≤ 2 days and photolysis products are known and/or identified, then assess photolysis products for environmental hazards.

Tier 2b. If t½ ≤ 2 days and photolysis products are not known and/or identifiable, then prepare a stock solution of the PMN chemical using the standard humic-containing solution described in the direct and indirect photolysis screening test [40 CFR 796.3765 (b)(2) and (c)(2)], expose to sunlight for at least 6 half-lives (t½), and test photolysis products for toxicity with the most sensitive species from the environmental base set.

Tier 3. Test for aerobic biodegradability according to any one of the following test guidelines:

Modified Sturm Test	40 CFR 796.3260
Closed Bottle Test	40 CFR 796.3200
Modified OECD Screening Test	40 CFR 796.3240
Modified MITI Test (I)	40 CFR 796.3220
Modified AFNOR Test	40 CFR 796.3180

In addition, if appropriate, physical/chemical properties including:

Log K_{ow} (40 CFR 796.1550, 796.1570, or 796.1720)
Vapor pressure (40 CFR 796.1950)
Boiling point (40 CFR 796.1220)
Melting point range (40 CFR 796.1300)

If the PMN chemical passes the aerobic biodegradability test according to the criteria set forth in the guidelines, no further testing may be recommended. A new risk assessment is conducted to determine if chronic ecotoxicity testing is warranted.

4. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR 797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% AI and mean measured concentrations; and statistical analysis of effective concentrations at days 7, 14, 21, and 28.

Daphnid chronic toxicity testing (40 CFR 797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21.

5. Ecotoxicity testing for release to terrestrial ecosystems.

The terrestrial base set of environmental toxicity tests (i.e., the early seedling growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

References:

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September, 1988; revised June, 1994

Category: Soluble complexes of Zinc

Definition. This category includes all organic and inorganic soluble complexes of zinc, for example, zincates, organozincs, such as, dimethylzinc. Not included in this category are zinc-complexed acid dyes and strong ion pairs between zinc and anionic surfactants. There are no toxicity data for soluble complexes of zinc, therefore, the toxicity data for the free Zn^{++} ion will be used to predict aquatic toxicity.

Hazard Concerns. Zinc produces acute toxicity to freshwater aquatic organisms over a range of concentrations from 90 to 58,100 ug/L and produces chronic toxicity over a range from 47 to 852 ug/L. The acute to chronic ratio (ACR) for Zn has been set at 3 in the water quality criteria (WQC) document. Zinc concentrations from 30 to 21,600 ug/L have been shown to reduce the growth of various aquatic plants and algae appear to be the most sensitive group. Bioconcentration factors (as logarithms) for freshwater fish ranged from 1.7 to 2.6, and from 2.0 to 3.1 for freshwater invertebrates. Zinc is an essential nutrient trace element which can be toxic at higher concentrations. While acute toxicity is affected by hardness, chronic toxicity is not affected. The freshwater criteria at an average hardness of 100 mg/L are 0.120 ug/L for acute exposures and 0.110 ug/L for chronic exposures; the saltwater criteria are 0.095 ug/L for acute exposures and 0.086 ug/L for chronic exposures. These criteria are based on toxicity information for the following Zn salts: sulfate, chloride, phosphate, and nitrate.

General Testing Strategy

To address ecotoxicity concerns, base set acute aquatic toxicity testing (algae: static method, daphnid and fish: flow-through method, all measured concentrations).

April, 1990

Definition. This category includes inorganic salts of zirconium (Zr), complexes between Zr and organic acids, and organoZr compounds, i.e., Zr covalently-bonded with carbon. For example, some inorganic Zr salts include: Zr sulfate, Zr oxychloride, and Zr tetrachloride. Not included in this category are dyes complexed with Zr.

Hazard Concerns. Soluble salts of Zr are known to be moderately toxic to green algae and fish based on exposures in soft water and in terms of mg Zr/L. Toxicity information are only available for Zr sulfate, Zr tetrachloride, and Zr oxychloride. The toxicity profile for Zr based on available toxicity data, mg Zr/L (ppm Zr), and moderate hardness (i.e., 150.0 mg/L as $CaCO_3$) is:

fish 96-h LC50 = 58.0 (n=3)
green algal 96-h EC50 = 2.6

Zirconium is more toxic in soft water than hard water. Acute toxicity to fish have been shown to increase 13 times as hardness decreases from 400.0 to 20 mg/L.

Boundaries. The toxicity of Zr compounds depends on the their physical/chemical properties and the hardness of receiving waters. The toxicity of Zr salts and Zr complexes with organic acids are expected to be related to their water solubility and MW. The toxicity of organoZr compounds are also expected to be related to their octanol/water partition coefficient (Kow).

The most important property determining the toxicity of Zr compounds is water solubility. Water solubility cannot be estimated accurately and has to be measured. The water solubility of organoZr compounds is expected to decrease as Kow increases. There is no lower bound for Kow and the upper bound cannot be determined at this time since the Kow fragment-constant for Zr is not known. In addition to solubility, MW is also an important boundary. Compounds with MWs > 1000 are not expected to be absorbed by aquatic organisms even if they are water soluble. Therefore, only Zr compounds with MWs < 1000 are expected to be toxic.

<u>General Testing Strategy</u>

I. <u>Release to Aquatic Ecosystems</u>

Tier 1. The <u>aquatic</u> base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR §797.1400) and daphnids (40 CFR §797.1300) will be done using the flow-through method; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; the total organic carbon (TOC) concentration of dilution water in the control must be less than 2.0 mg TOC/L; TOC must be measured in the control just prior to
the start of the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water

solubility of the compound beyond its aqueous solubility limit; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$. If toxicity mitigation testing is done with humic acid, then the static method with nominal concentrations will be recommended.

The algal toxicity testing (40 CFR §797.1050), should be done with the static method; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with no more than 0.300 mg/L EDTA as a final concentration; the TOC of the test/growth medium should be less than 2.0 mg TOC/L; TOC should be measured just prior to the start of the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; and solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the compound beyond its aqueous solubility limit. If toxicity mitigation testing is done with humic acid, then nominal concentrations will be recommended.

If there is no significant risk from the Zr compound after the results of the environmental base set have been integrated into the risk assessment, then no further testing will be recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR §797.1600), with the flow-through method; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; the TOC of dilution water in the control should be less than 2.0 mg TOC/L; TOC should be measured in the controls just prior to and during the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the compound beyond its aqueous solubility limit; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$.

Daphnid chronic toxicity testing (40 CFR §797.1330), with the flow-through method; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; the TOC of dilution water in the control should not exceed 2.0 mg TOC/L; TOC must be measured in the controls just prior to and during the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the compound beyond its aqueous solubility limit; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$.

II. <u>Release to Terrestrial Ecosystems</u>: The <u>terrestrial</u> base set of environmental toxicity tests will be recommended for terrestrial exposures. The terrestrial base set includes: the early seeding growth test (40 CFR 797.2800), the earthworm toxicity test (40 CFR.795.150), the soil microbial community bioassay (40 CFR 797.3700), and the avian acute oral toxicity test (40 CFR 797.2175). Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test (40 CFR 797.xxxx), the plant uptake test (40 CFR 797.2850), and the avian reproduction test (40 CFR 797.2130 for bobwhite quail or 40 CFR 797.2150 for mallard duck).